Neurology

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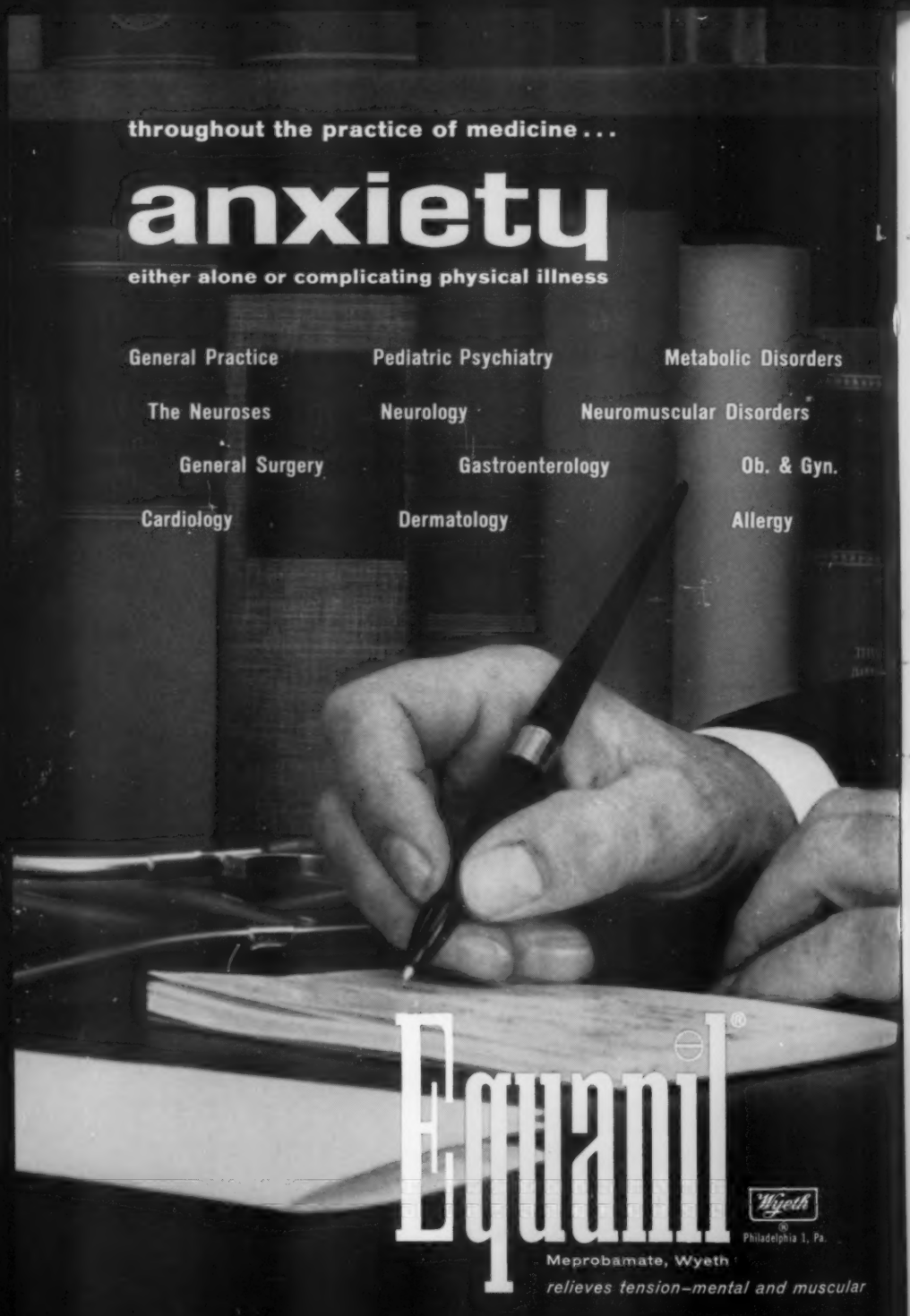
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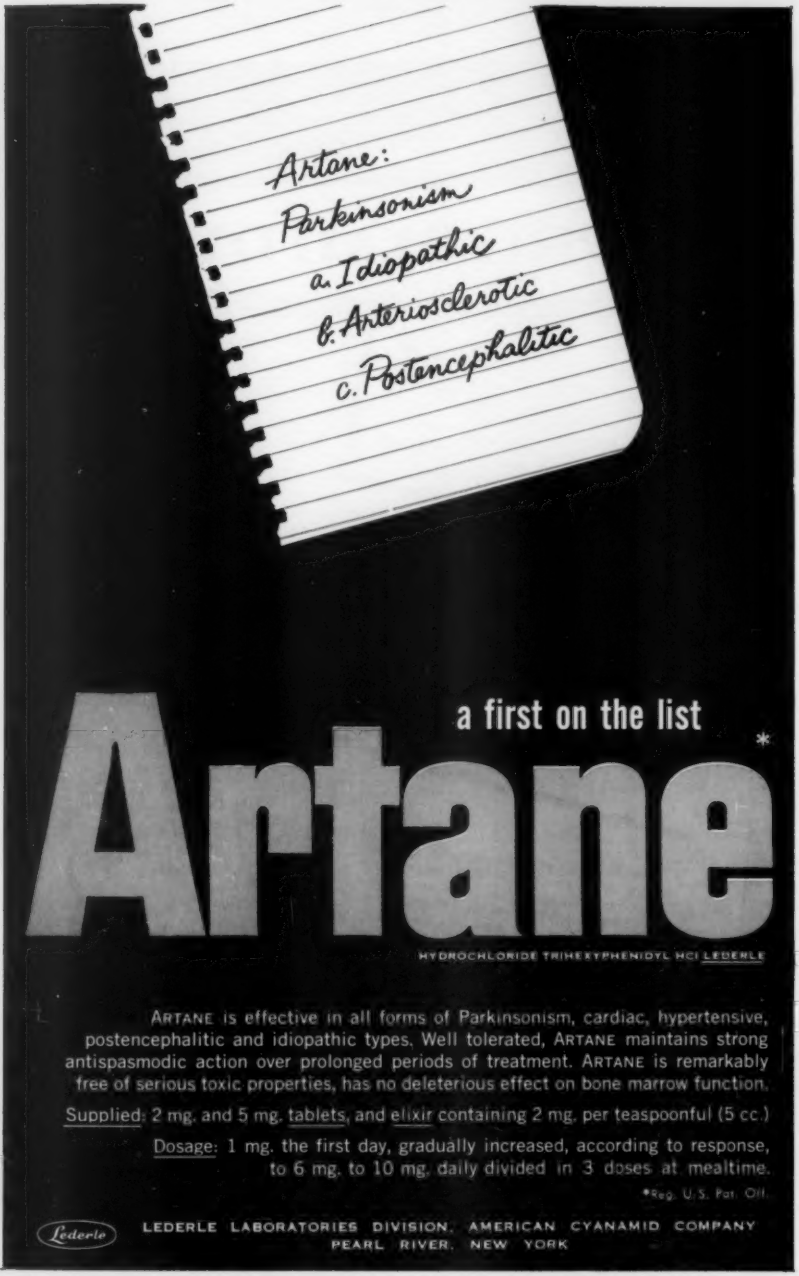
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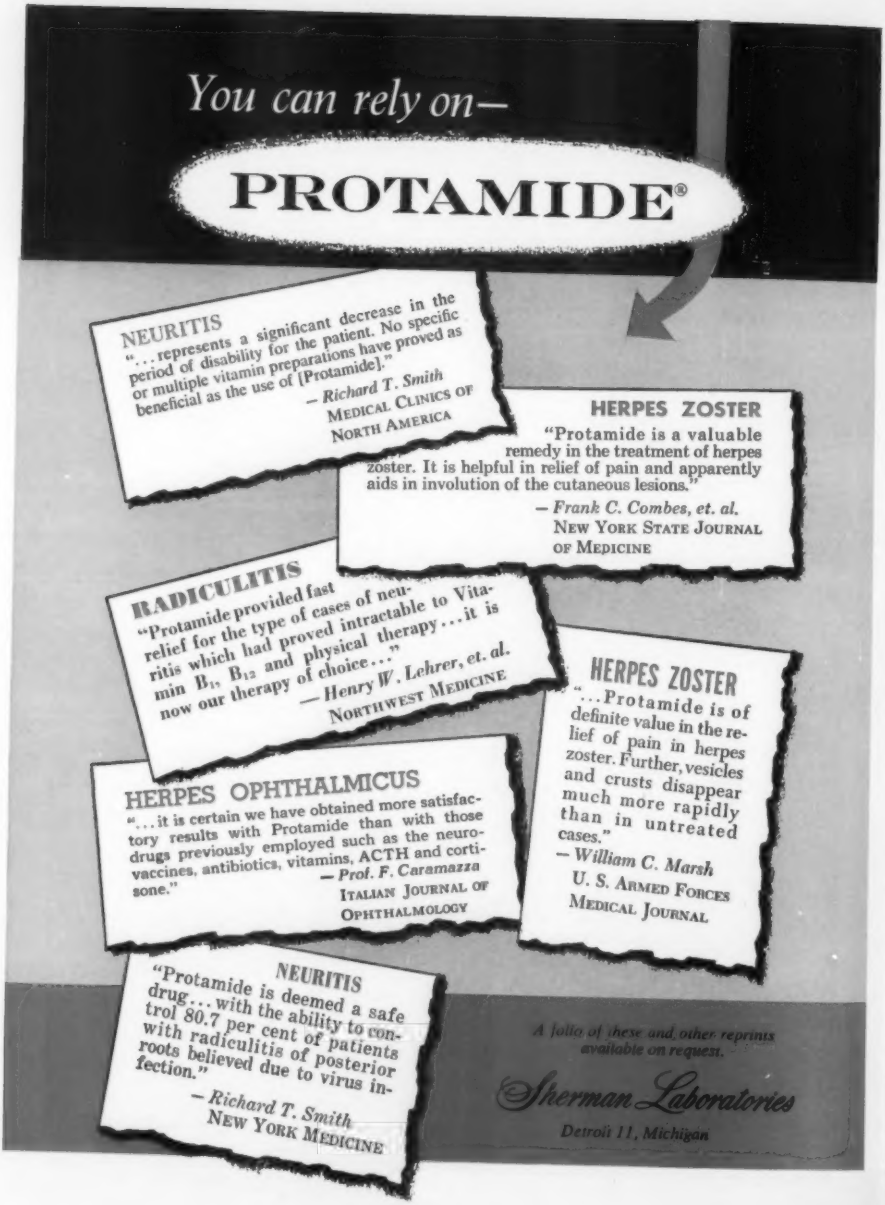
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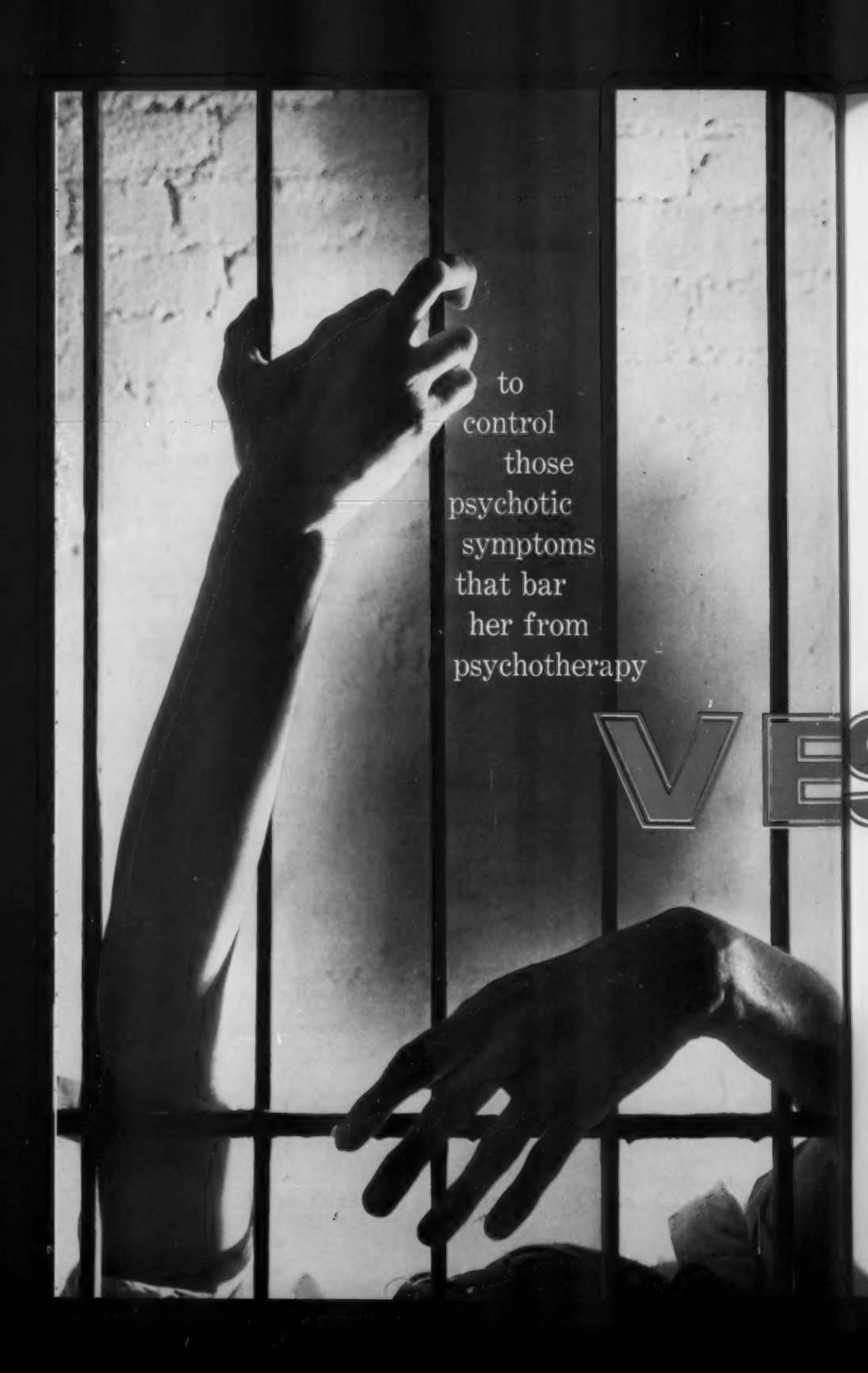
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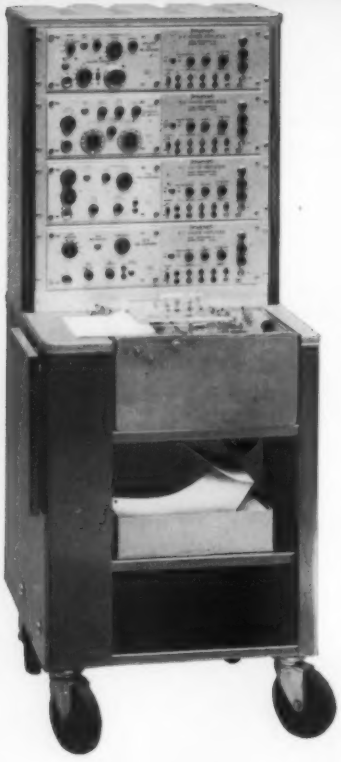

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STUDY 2[2]		"pronounced"			
Herniated disc	39	25	13	—	1
Ligamentous strains	8	4	4	—	—
Torticollis	3	3	—	—	—
Whiplash injury	3	2	1	—	—
Contusions, fractures, and muscle soreness due to accidents	5	3	2	—	—
STUDY 3[5]		"excellent"			
Herniated disc	8	6	2	—	—
Acute fibromyositis	8	8	—	—	—
Torticollis	1	—	—	1	—
STUDY 4[6]		"significant"			
Pyramidal tract and acute myalgic disorders	30	27	—	2	1
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Treatment of anticholinesterase intoxication with oximes

David Grob, M.D.,* and Richard J. Johns, M.D.

MANY INSTANCES OF SERIOUS and even fatal intoxication by anticholinesterase compounds have occurred in normal subjects after accidental exposure to organophosphorus insecticides such as parathion and chemical warfare agents such as sarin ("nerve gas") and in patients with myasthenia gravis after overtreatment with organophosphorus compounds such as octamethyl pyrophosphoramide (OMPA) or quaternary ammonium compounds such as neostigmine, pyridostigmine (Mestinon), or ambenomium (Mytelase).[1] The manifestations of intoxication by any of these agents are quite similar, consisting of increased activity of smooth muscle and secretory glands, central neural symptoms, muscular weakness, and fasciculations in normal subjects and increased strength followed by weakness in patients with myasthenia gravis (Table 1). The administration of large doses of atropine ameliorates the smooth muscle, secretory, and central neural effects but has little or no influence on weakness due to neuromuscular block. This block is attributable to the accumulation of acetylcholine at the motor end plates after the arrival of each motor nerve impulse, resulting in persistent depolarization of the end-plate region. In severe anticholinesterase intoxication, death occurs as a result of paralysis of the muscles of respiration and of the pharynx and tongue unless artificial respiration and an open airway are maintained until spontaneous recovery occurs (Table 2). There has been no clinically useful means of accelerating recovery from the neuromuscular block.

During the past two years, Wilson and others[2–4] have demonstrated that cholinesterase inhibition, neuromuscular block, and lethal effects produced by organophosphorus anticholinesterase compounds in experimental animals may be reversed by a number of oximes, including pyridine-2-aldoxime methiodide (2-PAM) and diacetyl monoxime (DAM) (Fig. 1). While cholinesterase reactivation by oximes in vitro is most striking after inhibition by organophosphorus anticholinesterase compounds such as sarin, less marked reactivation can also be demonstrated after inhibition by quaternary ammonium anticholinesterase compounds such as neostigmine, pyridostigmine (Mestinon), and, possibly, ambenomium (Mytelase). Both protective and reactivative effects on cholines-

From the Department of Medicine, Johns Hopkins University and Hospital, Baltimore, Maryland.

Presented at the annual meeting of the American Academy of Neurology, April 25, 1958.

This work was supported by a contract between the Johns Hopkins University and the U. S. Army Chemical Corps, and was aided by grant B-894(2) from the Division of Neurologic Diseases and Blindness, National Institute of Health, U.S.P.H.S.

*Present address: State University of New York College of Medicine and Maimonides Hospital, Brooklyn.

TABLE 1
SIGNS AND SYMPTOMS OF NERVE GAS POISONING

Site of action	*Signs and Symptoms*
	AFTER LOCAL EXPOSURE
Muscarine-like	
Pupils	Miosis, marked, usually maximal (pin point), sometimes unequal
Ciliary body	Frontal headache; eye pain on focusing; slight dimness of vision; occasional nausea and vomiting
Conjunctivae	Hyperemia
Nasal mucous membranes	Rhinorrhea; hyperemia
Bronchial tree	Tightness in chest, sometimes with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, cough
	AFTER SYSTEMIC ABSORPTION
Bronchial tree	Tightness in chest, with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion; dyspnea; slight pain in chest; increased bronchial secretion; cough; pulmonary edema; cyanosis
Gastrointestinal	Anorexia; nausea; vomiting; abdominal cramps; epigastric and substernal tightness (? cardiospasm) with "heartburn" and eructation; diarrhea; tenesmus; involuntary defecation
Sweat glands	Increased sweating
Salivary glands	Increased salivation
Lacrimal glands	Increased lacrimation
Heart	Slight bradycardia
Pupils	Slight miosis, occasionally unequal; later more marked miosis
Ciliary body	Blurring of vision
Bladder	Frequency, involuntary micturition
Nicotine-like	
Striated muscle	Easy fatigue; mild weakness; muscular twitching; fasciculations; cramps; generalized weakness, including muscles of respiration, with dyspnea and cyanosis
Sympathetic ganglia	Pallor; occasional elevation of blood pressure
Central nervous system	Giddiness; tension; anxiety; jitteriness; restlessness; emotional lability; excessive dreaming; insomnia; nightmares; headache; tremor; withdrawal and depression; bursts of slow waves of elevated voltage in electroencephalograph, especially on overventilation; drowsiness; difficulty concentrating; slowness of recall; confusion; slurred speech; ataxia; generalized weakness; coma, with absence of reflexes; Cheyne-Stokes respiration; convulsions; depression of respiratory and circulatory centers, with dyspnea, cyanosis, and fall in blood pressure

terase enzymes of human plasma, red cells, muscle, and brain in vitro were noted with 2-PAM, while DAM had only protective effect (Table 3). Therefore, studies were carried out on the influence of administration of oxime on neuromuscular block and intoxication due to organophosphorus anticholinesterase compounds, including sarin, and to quaternary ammonium compounds, including neostigmine.[5,6]

Initial observations were made on the effect of intraarterially administered oxime on the local neuromuscular block produced by the intraarterial injection of these and other anticholinesterase compounds. Studies were then made on the effect of intravenously administered oxime on systemic anticholinesterase intoxication. Muscle function was measured by percutaneous electrical stimulation of the ulnar nerve and recording the evoked muscle action potentials and isometric tension from the adductor pollicis brevis.[7] The standard pattern consisted of trains of 4 stimuli at intervals of 40 msec. delivered every five seconds. In normal subjects, each train of stimuli evoked

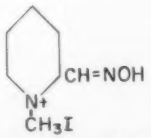
TABLE 2
MEASURES FOR TREATMENT OF INTOXICATION DUE TO ORGANIC PHOSPHATE ANTICHOLINESTERASE COMPOUNDS

Patient	Anticholinesterase compound	Symptoms	Atropine administered* Route	Total dose (mg.)	Time (hrs.)	Suction	Intubation	Artificial respiration
H.B.	Sarin	moderately severe	I.M.	6.5	13	0	0	0
A.S.	Sarin	moderately severe	I.M.	16	48	0	0	0
M.B.	Sarin	moderately severe	I.V. and I.M.	15	28	0	0	0
A.M.	Sarin	very severe	I.V. and I.M.	21	39	+	0	+
A.R.	TEPP†	very severe	I.V. and I.M.	24	24	+	+	+
C.B.	OMPA‡	very severe	I.V. and I.M.	50	24	+	+	+

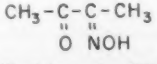
*Atropine was administered in doses of 1 to 2 mg. as frequently as needed to alleviate the muscarine-like and central neural effects of the anticholinesterase compound. All patients recovered.
†Tetraethyl pyrophosphate
‡Octamethyl pyrophosphoramide

TABLE 3
EFFECT OF VARIOUS ANTICHOLINESTERASE COMPOUNDS ON THE ABILITY OF 2-PAM AND DAM TO PROTECT AND REACTIVATE CHOLINESTERASE

Anticholinesterase compound (10^{-7} to 10^{-5}M)	Per cent protection by: 2-PAM (10^{-6} to 10^{-4}M)	DAM (10^{-5} to 10^{-3}M)	Per cent reactivation by: 2-PAM (10^{-6} to 10^{-4}M)	DAM (10^{-5} to 10^{-3}M)
Neostigmine	18	16	11	6
Pyridostigmine	13	8	7	3
Ambenomium	3	3	6	2
Sarin	39	14	44	1



Pyridine-2-aldoxime methiodide (2-PAM)



Diacetyl monoxime (DAM)

Fig. 1. Formulas of two oximes used in the treatment of anticholinesterase intoxication

muscle action potentials of equal amplitude and twitch tension of normal amplitude. After administration of sufficient anticholinesterase compound to produce neuromuscular block, there was progressive depression of successive muscle action potentials and reduction in twitch tension.[8] This local neuromuscular block produced by neostigmine, pyridostigmine, ambenomium, or sarin was promptly and strikingly reversed after intraarterial injection of 0.05 mg. of 2-PAM or DAM; muscle action potentials and tension were restored to their initial amplitude. The time course of the neuromuscular block produced by anticholinesterase compounds may be shown by plotting amplitude of the first and fourth potentials of the train evoked every five seconds against time. After the intraarterial injection of neostigmine, sarin, or any of the other compounds studied, the fourth potential of each train was markedly depressed for ten to thirty minutes and then gradually returned to normal over a period of about an hour (Fig. 2). The first potential of each train was reduced to a lesser degree. The depression of all evoked potentials was reversed one to three minutes after the intraarterial injection of 0.05 or 0.1 mg. of 2-PAM or DAM (Figs. 3 and 4). These oximes also protected against the neuromuscular blocking action of the anticholinesterase compounds.

Systemic effects of anticholinesterase compounds were then produced in normal volunteer subjects by the oral or parenteral admin-

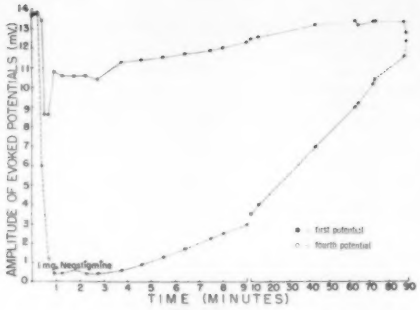


Figure 2

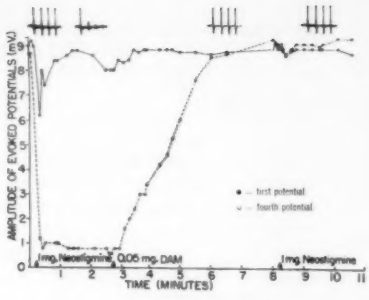


Figure 3

Fig. 2. Time course of the depressant effect of intraarterial injection of neostigmine on evoked muscle action potentials in a normal subject. The amplitude of the first and fourth potentials in response to a train of 4 nerve stimuli 40 msec. apart evoked every five seconds has been plotted.

Fig. 3. Reversal by intraarterially injected DAM of the depressant action of neostigmine on evoked muscle action potentials in a normal subject and inhibition by DAM of the depressant effect of a second injection of neostigmine. The amplitude of the first and fourth potentials in response to a train of 4 nerve stimuli 40 msec. apart evoked every five seconds has been plotted.

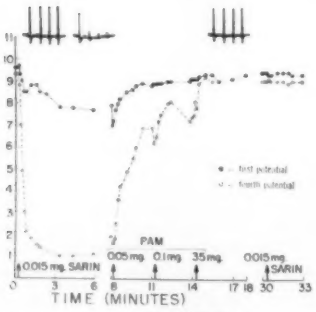


Figure 4

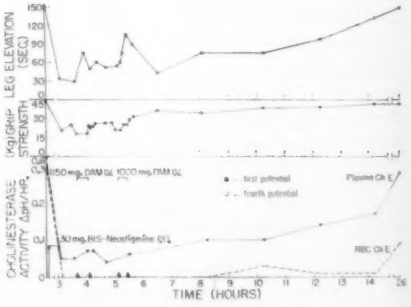


Figure 5

Fig. 4. Reversal by intraarterially injected 2-PAM of the depressant effect of sarin on evoked muscle action potentials in a normal subject and inhibition by 2-PAM of the depressant effect of a second injection of sarin. The amplitude of the first and fourth muscle action potentials in response to a train of 4 nerve stimuli 40 msec. apart evoked every five seconds has been plotted.

Fig. 5. Reversal by DAM and 2-PAM of generalized weakness produced by bis-neostigmine in a normal subject and transient reversal of plasma cholinesterase inhibition.

istration of graded doses until generalized weakness and muscular fasciculations occurred, accompanied by gastrointestinal symptoms and sweating. The intravenous injection of 1,000 to 2,000 mg. of 2-PAM or DAM over a period of five to ten minutes ameliorated the weakness to a moderate degree, as indicated by improvement in swallowing and speech, grip strength, and length of time the head or each extended leg could be elevated from the supine position or the arms from the sitting position (Fig. 5). Muscular fasciculations were reduced to a lesser degree. The improvement began within thirty seconds after injection and was maximal in five to ten minutes. Approximately twenty minutes later, there was usually some

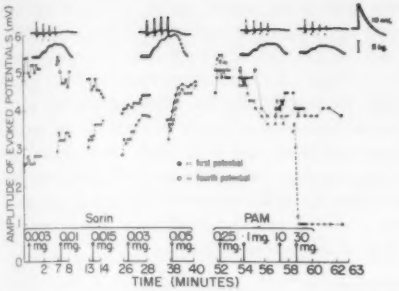


Figure 6

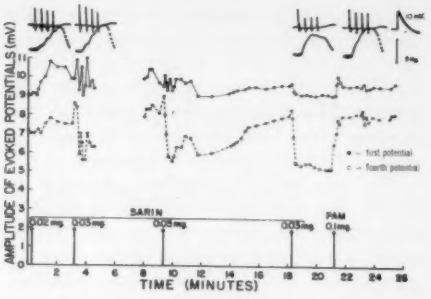


Figure 7

Fig. 6. Reversal by intraarterially injected 2-PAM of the reparative effect of sarin on evoked muscle action potentials and tension in a myasthenic patient. The amplitude of the first and fourth potentials in response to a train of 4 nerve stimuli 40 msec. apart evoked every five seconds has been plotted.

Fig. 7. Reversal by intraarterially injected 2-PAM of the depressant effect of excessive sarin on evoked muscle action potentials and tension in a myasthenic patient. The latter had been preceded by the reparative effect of previous injections of sarin. The amplitude of the first and fourth potentials in response to a train of 4 nerve stimuli 40 msec. apart evoked every five seconds has been plotted.

return of weakness and fasciculations but not to the original level. Another injection of oxime resulted in further improvement. In no instance was there a dramatic increase in strength comparable to the local reversal of neuromuscular block observed after intraarterial injection of much smaller doses of oxime.

In myasthenic patients there was generalized weakness and defective neuromuscular transmission before the administration of an anticholinesterase agent, as indicated by progressive decline in the amplitude of successive evoked muscle action potentials (Figs. 6 and 7).[9] The administration of an appropriate dose of anticholinesterase compound improved strength and neuromuscular transmission. Subsequent intraarterial or intravenous injection of 2-PAM or DAM reversed this effect, resulting in a return toward the original state of weakness (Fig. 6).

When the myasthenic patients were administered an excess of anticholinesterase compound, the initial improvement was followed by a decrease in strength and neuromuscular transmission, resembling the weakness and neuromuscular block produced by anticholinesterase compounds in normal subjects. The subsequent intraarterial or intravenous administration of 2-PAM or DAM reversed this effect, again as in normal subjects, resulting in an increase in strength and in the amplitude of evoked potentials (Fig. 7). The doses of oxime required and the degree of change were similar to those in normal subjects. However, whereas in normal subjects the further administration of the same dose of oxime after recovery from the effects of the anticholinesterase compound produced no change, in myasthenic patients, this resulted in depression of strength and neuromuscular transmission toward the level that had existed before administration of anticholinesterase compound. Hence, more cautious administration of oxime was necessary in myasthenic patients than in normal persons.

In both normal and myasthenic subjects, 2-PAM and DAM were equally effective and the action of each of the anticholinesterase compounds was influenced to the same degree. This was in contrast to marked differences between the oximes and between various anticholinesterase compounds in the reversal of the cholinesterase inhibition in vitro.

In both normal and myasthenic subjects, the intravenous administration of 1,000 to 2,000 mg. of 2-PAM or DAM produced slight to moderate reversal of plasma and red blood

cell cholinesterase inhibition but had no effect on the gastrointestinal symptoms, sweating, salivation, bradycardia, or central neural symptoms produced by the anticholinesterase compounds. Therefore, the oximes must be used in conjunction with atropine in the management of anticholinesterase intoxication.

The only undesirable effects observed occurred after intravenous injection of DAM at a rate faster than 60 mg. per minute. This resulted in a burning sensation radiating up the injected vein, followed by moderate giddiness, drowsiness, a sensation of warmth and tingling in the abdomen and chest, and a slight reduction in blood pressure and increase in cardiac rate, recumbent and standing. These effects lasted for one to five minutes after cessation of the injection. Intravenous injection of DAM at a slower rate, or of 2-PAM at a rate up to 300 mg. per minute, resulted in no local or systemic signs or symptoms except for slight tachycardia on standing. Since 2-PAM can be injected more rapidly than DAM, it may prove to be the more useful of the two oximes. However, the intraarterial injection of 20 mg. or more of 2-PAM in the absence of anticholinesterase compound produced transient local weakness and neuromuscular block. After intraarterial injection of an anticholinesterase compound, this neuromuscular blocking action of high concentrations of 2-PAM was more marked. No such effect was noted with DAM, and neither compound produced weakness with intravenous injection of 2,000 mg. It is not yet clear which oxime will prove to be the safer and more useful agent nor is it known what the maximally tolerated doses and toxic doses are in man. Nevertheless, it is clear that these oximes do accelerate recovery from muscular weakness due to intoxication by anticholinesterase compounds in normal and myasthenic subjects and it is likely that their use, in conjunction with atropine, will diminish the necessity for or duration of artificial respiration and endotracheal intubation in the management of this intoxication.

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Clinical significance of 14 and 6 per second positive spike complexes

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EVER SINCE the Gibbses discussed 14 and 6 per second positive spike complexes in 1951,[1] electroencephalographers have disagreed as to the clinical significance of this pattern. It has been called artefactual by some and pathologic by others. There has, however, been general agreement that [1] this pattern is most likely to be seen in children, adolescents, and young adults and [2] the complexes are almost always seen during sleep. The Gibbses felt that these discharges originated in the thalamus and hypothalamus and that they represented a distorted form of the normal sleep pattern. The great majority of their patients had some sort of epileptiform disorder.

It is the purpose of this paper to correlate the 14 and 6 per second positive spike complexes in a series of routine electroencephalographic records with the clinical conditions of the patients.

MATERIAL, METHOD, AND RESULTS

An 8-channel, ink-writing standard Grass machine was used throughout. Monopolar leads were used with the electrode placement customarily employed by Gibbs. The reference leads included those to both ears (both mastoids in young children), the nose, and the low midoccipital region. A record taken during natural or drug-induced sleep was obtained on every patient. Seconal, Nembutal, or chloral hydrate was administered. Whenever possible, records were also taken with the patient awake and after a period of hyperventilation.

All electroencephalographic records taken between April 1, 1956, and April 1, 1958, were reviewed for the 14 and 6 per second positive spike complexes. Records of both inpatients and outpatients were referred to. A variety of the ailments frequently encountered in a general hospital and its outpatient service, including the pediatric and psychiatric sections, was represented. All clinical information was gathered from the histories supplied by the patients' physician on the form requesting electroencephalographic examination.

A total of 2,209 electroencephalographic records were obtained during this period of time. The age and sex distribution, the number of normal and of abnormal or borderline records, and the incidence of positive spike complexes in those records are shown in Table 1. The positive spike complexes composed 6.4% of all records and 10.5% of abnormal or borderline records.

Positive spikes appear in over one-fourth of the abnormal or borderline records of patients aged 11 to 20 years – a peak incidence. The first and third decades show approximately the same incidence, both being somewhat higher than the over-all average. No positive spike complexes were seen in patients under the age of 1 year or above the age of 60. Further subdivision shows that the incidence of positive spike complexes increased markedly in the 6- to 10-year age group (Table 2).

The 142 records showing positive spikes were obtained in 136 patients, 65 records being from male patients and 77 from female. The complexes usually were seen simultaneously in the occipital and temporal leads or just in the temporal leads. They appeared either unilaterally or bilaterally, without definite pattern even in a single record. They were invariably observed when the patient was asleep and on the portion of the recording made with the nose reference lead. In only 2 instances were they seen on electroencephalograms when the patient was awake as well.

In 60 of the 136 patients, the 14 and 6 positive spike complex was the only electroencephalographic alteration noted; in 76 patients,

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TABLE 1

INCIDENCE OF 14 AND 6 PER SECOND POSITIVE SPIKE COMPLEXES

Age group (years)	Total electro-encephalo-grams	Normal records	Abnormal or borderline records	Positive spike complexes		
				Incidence	Per cent of total records	Per cent of abnormal or borderline records
0 to 10	483	109	374	44	9.1	11.8
11 to 20	368	109	259	66	17.9	25.2
21 to 30	254	104	150	19	7.5	12.7
31 to 40	285	149	136	6	2.1	4.4
41 to 50	304	136	168	4	1.3	2.4
51 to 60	287	145	142	3	1.0	2.1
61 to 70	168	72	96	0	0	0
Over 70	60	28	32	0	0	0
Totals	2,209	852	1,357	142*	6.4	10.5

*This total includes serial records on 4 patients. Of the 142 records with positive spikes, 65 were from male and 77 from female patients.

TABLE 2

INCIDENCE OF THE 14 AND 6 PER SECOND POSITIVE SPIKE COMPLEX IN PATIENTS LESS THAN 21 YEARS OF AGE

Age group (years)	Total electro-encephalo-grams	Normal records	Abnormal or borderline records	Positive spike complexes		
				Incidence	Per cent of total records	Per cent of abnormal or borderline records
0 to 1	22	3	19	0	0	0
1 to 5	257	69	188	13	5.1	6.9
6 to 10	204	37	167	31	15.4	18.5
11 to 20	368	109	259	66	17.9	25.2
Total	851	218	633	110	13.0	17.5

TABLE 3

ASSOCIATED ELECTROENCEPHALOGRAPHIC ABNORMALITIES IN 76 OF 136 PATIENTS WITH POSITIVE SPIKE COMPLEXES

Abnormality	No. of records
Focal slowing	24
Focal spike discharges	23
Nonfocal slowing	16
Focal slow waves and spikes	9
Random, nonfocal spikes	7
Abnormal response to HV	7
Paroxysmal, nonfocal spike-domes	4
Random slow waves and spikes	3
Depressed electrical activity, focal	1

other abnormalities were associated (Table 3). These abnormalities occurred both singly and in combinations.

The clinical manifestations exhibited by the patients were divided into three main groups (Table 4). Group one was composed of 58 patients with *clinical convulsions*. In each case, there was a definite history of a grand mal or psychomotor convulsion (Fig. 1). There were no patients with an acceptable history of petit mal.

The second group consisted of 55 patients suffering from a wide variety of *epileptic equivalents*. These were of three types. In the first, the history was suggestive of periodic autonomic or visceromotor discharges (Fig. 2); the second type was represented by 5 pa-

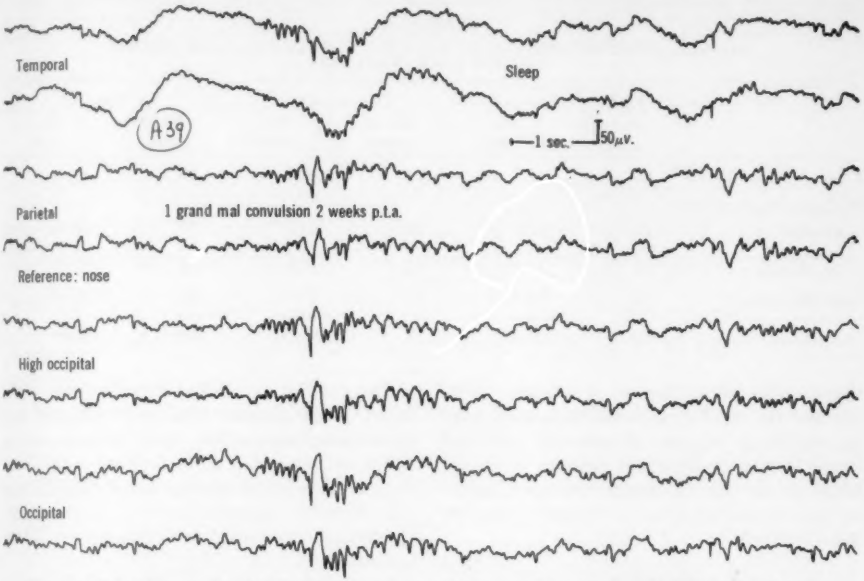

Fig. 1. This 11-year-old girl had her first generalized convulsion two weeks before examination. The monopolar recording shows bilateral 14 per second positive spikes with a single 6 per second spike.

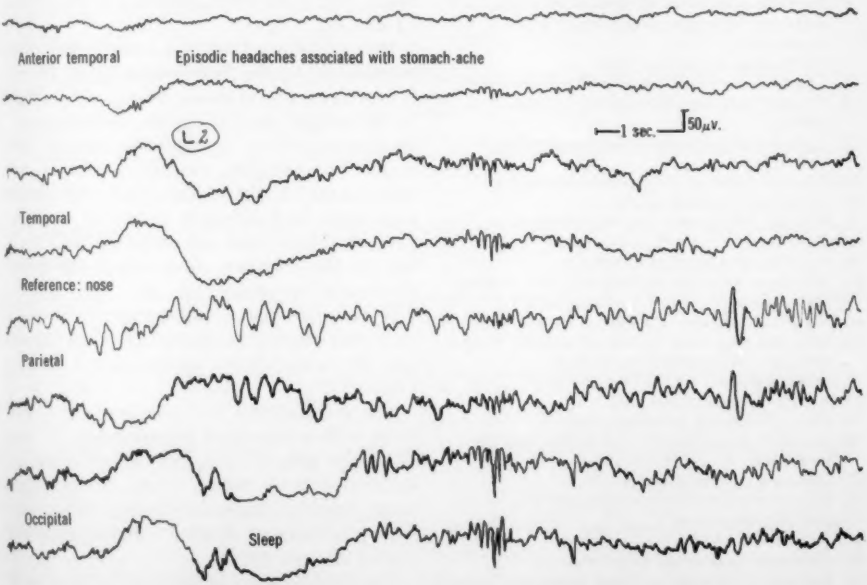

Fig. 2. A 12-year-old boy with a two-year history of episodes of headaches associated with abdominal pain. This monopolar recording shows bilateral 14 per second positive spikes predominating in the occipital leads.

TABLE 4

CLINICAL MANIFESTATIONS IN 136 PATIENTS WITH 14 AND 6 PER SECOND POSITIVE SPIKE COMPLEXES

	Positive spikes only			*Combinations*			*Total*		
	No. of cases	*Per cent*		*No. of cases*	*Per cent*		*No. of cases*	*Per cent*	
Clinical convulsions	24	40.0		34	44.7		58	42.6	
Epileptic equivalents									
Clinical	11	18.3		16	21.0		27	19.8	
Migraine	3	5.1	41.7	2	2.7	39.5	5	3.6	40.4
Psychiatric	11	18.3		12	15.8		23	17.0	
	25			30			55		
Miscellaneous	11	18.3		12	15.8		23	17.0	
Totals	60	100.0		76	100.0		136	100.0	

tients with a strong history of migraine (Fig. 3); and the third type included patients with psychiatric or behavior disturbances who had never had an epileptiform disorder (Fig. 4). Some of the clinical manifestations exhibited by patients included in this second group are listed in Table 5.

TABLE 5

CLINICAL MANIFESTATIONS EXHIBITED BY 55 PATIENTS WITH EPILEPTIC EQUIVALENTS

1. Episodic occurrence of dreamlike states, outbursts of anger, argumentativeness, hyperactivity
2. Intermittent abdominal pain
3. Episodes of violent, uncooperative behavior
4. Temper tantrums and cyanosis (cardiac anomaly)
5. Episodes of automatic behavior, possible narcolepsy
6. Syncope followed by generalized tingling
7. Crying and shaking spells
8. Periods of blankness and disorientation
9. Fainting, dizzy, or black-out spells
10. Episodes of numbness of sides
11. Impulsive behavior, chronic runaway, writing bad checks
12. Vomiting followed by deep sleep and amnesia
13. Slow learning, poor school adjustment, temper tantrums, destructiveness, juvenile schizophrenia(?)
14. Attacks of unlocalized pain
15. Excessive crying, behavior problem
16. Enuresis, hyperactivity, dissociative type of disorder
17. Insomnia, psychoneurosis
18. Sudden tremulousness of face, left arm, and leg, hysteria(?)
19. Episodes of nausea and vomiting
20. Dizziness, abdominal pain, lethargy
21. Behavior disturbance, school problems, hyperactivity

The third group, called *miscellaneous*, consisted of 23 patients who were referred for electroencephalographic study because of a variety of nonepileptiform cerebral manifestations or in order to rule out some possible but not clinically apparent cerebral involvement. Conditions represented in this group are listed in Table 6.

No significant clinical difference between patients whose electroencephalograms show positive spikes alone or positive spikes combined with some other abnormality was noted (Table 4).

On an etiologic basis, 4 categories were distinguished. In the first, consisting of 27 patients, there was evidence of *organic damage to the central nervous system*, including pre- or perinatal anoxic or traumatic damage, encephalitis, meningitis, vascular anomalies, severe mental retardation associated with neurologic signs, lead poisoning in infancy, and intracerebral hematoma and excluding head trauma. In this category, there was a significant percentage difference between the patients who had only positive spikes and those with associated electroencephalographic abnormalities, the latter being a more frequent finding (Table 7).

The next category was composed of 20 patients with a history of *head trauma*. It was extremely difficult to assess the presence or severity of brain injury. None of these patients, however, showed neurologic signs suggesting permanent structural damage to the central nervous system.

The third category included 12 patients with *systemic disease* such as diabetes, hyperthy-

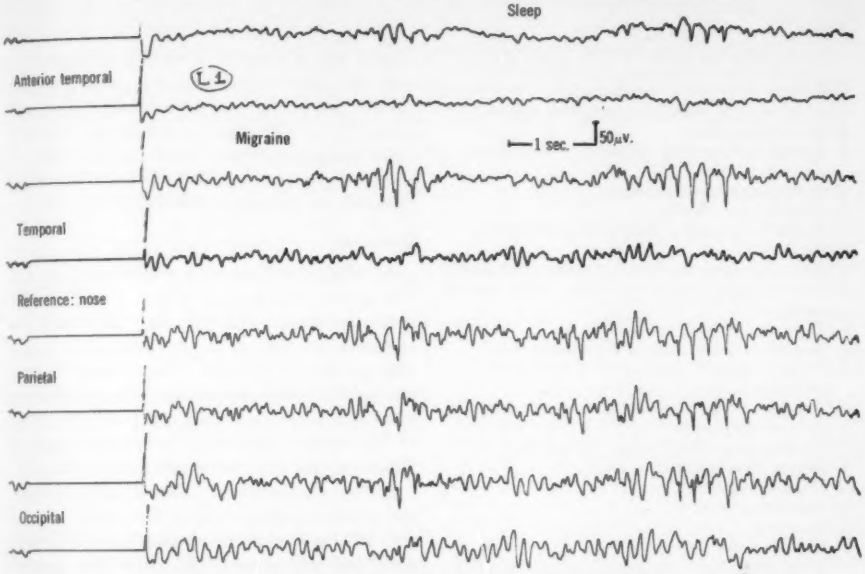

Fig. 3. A 28-year-old woman with a seventeen-year history of migraine. The monopolar recording reveals predominantly 6 per second positive spikes appearing on the left side.

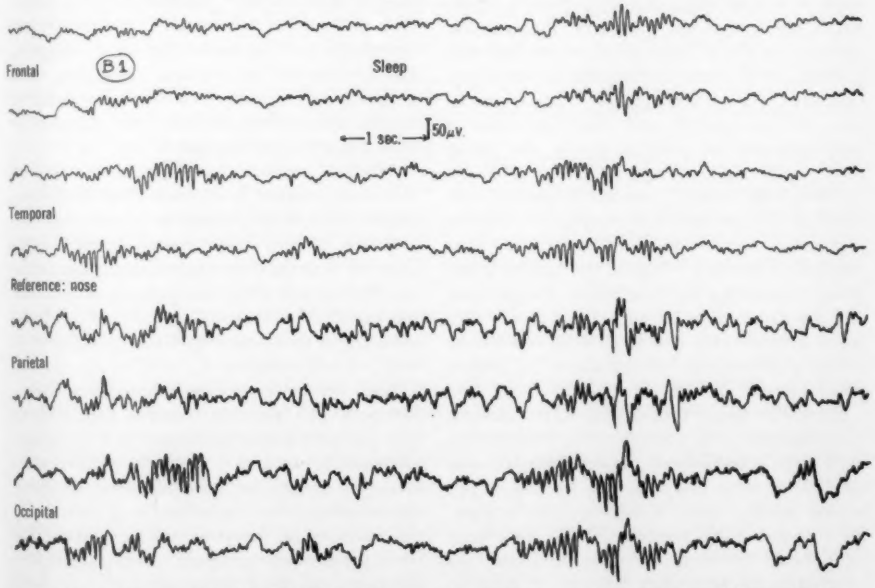

Fig. 4. A 10-year-old girl with idiopathic mental retardation and emotional problems characterized by temper tantrums, disobedience, and hyperirritability. She had never had epileptiform seizures. This monopolar recording shows bilateral 14 per second positive spikes.

TABLE 6
CONDITIONS REPRESENTED IN 23 PATIENTS INCLUDED IN MISCELLANEOUS GROUP

1. Numbness of right face, temporal arteritis(?)
2. Congenital alexia
3. Speech and hearing disturbance in brain-damaged child
4. Posttraumatic headaches
5. Huntington's chorea
6. Inability to speak in 9-year-old paraparetic child
7. Brain-damaged child with spastic quadriplegia
8. Left hemiatrophy of the body, right parietal angioma
9. Right temporal hematoma
10. Impaired vision, mental retardation(?)
11. Sudden onset of right-sided weakness in 23-year-old man
12. Head injury with unconsciousness, no sequelae, routine check-up
13. Cardiac anomalies, routine preoperative study
14. Retinal degeneration
15. Hyperthyroidism
16. Pulseless disease
17. Diabetes
18. Hepatic coma (cirrhosis)
19. Polyneuropathy

roidism, hepatic coma due to Laennec's cirrhosis, phenylketonuria, pulseless disease and polyneuropathy of undetermined etiology and patients who were undergoing routine preoperative study for congenital cardiac anomalies. In the second and third categories, a preponderance of patients are in the group with positive spike complexes only (Table 7).

The fourth category, termed *idiopathic*, consisted of 77 patients. The etiology of diseases represented could not be detected from the physicians' histories. This is the largest single group, accounting for over half of the patients, and the distribution between the patients with positive spikes only and those with other electroencephalographic abnormalities is almost equal (Table 7).

Particular attention was paid to the electroencephalograms of patients with behavior or psychiatric disturbances. These records made up 17% of those showing the 14 and 6 per second positive spike complexes. In evaluating this group, we reexamined the records of all patients between the ages of 1 and 20 referred to the laboratory because of behavior disturbances (Table 8). Of 146 patients, 108 (74%) had abnormal or borderline electroencephalographic records. Of 829 records obtained on all patients between the ages of 1 and 20 years referred to the laboratory for routine study, the same percentage, 74%, was found to be abnormal or borderline. Positive spike complexes were found in 110 (18%) of the total group and in 34 (31.4%) of the group referred for psychiatric reasons.

DISCUSSION

In 1951, the Gibbses first discussed the significance of the 14 and 6 per second positive spike complexes, although they had noted the existence of this type of discharge in their atlas published in 1948. They found the pattern in the sleep records of 312 out of 5,000 known or suspected epileptics and in 8 (2.7%) of 300 control subjects. The wake records of almost all these patients had been normal.

Over one-third of the 312 patients with positive spikes on sleep records had fainting spells, and 49% had some sort of convulsion. Classical petit mal was absent, but 2% of the patients had psychomotor seizures and 46% had generalized grand mal seizures. The most usual aura of patients with positive spike complexes was pain, but visceromotor and vegetative symptoms such as pounding heart, gagging, and so on were all common. Many of these patients were believed to have psychomotor attacks. Some were assaultive and 4 had committed murder during rage attacks.

Presthus and associates[2] found this type of electrical complex in at least 38 of 1,463 patients. Only those patients in whose sleep records the 14 and 6 per second positive spike complex was the only abnormality found were recorded. Only 18 of his patients were under the age of 20. His incidence of 2.6% is almost identical to that found by Gibbs and Gibbs in their control subjects.

High incidences of headache (16 patients), dizziness (15 patients), grand mal seizures (14 patients), and gastrointestinal symptoms (8 patients) as well as behavior disturbances, syncope, anxiety, hypersomnia, and vasomotor disturbances were recorded by Presthus. In the majority of the patients, these symptoms were paroxysmal in nature. Encephalitis was diagnosed in 2 of them, 10 had had head injury with concussion, and 4 had had injury to the head without concussion.

TABLE 7

POSSIBLE ETIOLOGIC FACTORS IN PATIENTS WITH THE 14 AND 6 PER SECOND SPIKE COMPLEX ABNORMALITY

	Positive spikes only		*Combinations*		*Total*	
	No. of cases	*Per cent*	*No. of cases*	*Per cent*	*No. of cases*	*Per cent*
Organic disease of the central nervous system	7	11.7	20	26.3	27	19.8
Trauma	11	18.4	9	11.8	20	14.6
Systemic disease	8	13.3	4	5.3	12	9.0
Idiopathic	34	56.6	43	56.6	77	56.6
Totals	60	100.0	76	100.0	136	100.0

Kellaway and associates[3] reported on awake and sleep electroencephalograms performed on a series of 950 normal children and found the 14 and 6 per second positive spike complex in 2.2%, a figure which accords well with those of the 2 series presented above.[2,3] Records of 200 children showing this pattern, all under the age of 16, were analyzed by Kellaway and associates, and they stated, "The clinical correlates of the abnormality are primarily recurrent paroxysmal episodes of autonomic, pain or behavioral type. . . . Headaches and/or abdominal pain with associated symptoms of dizziness, weakness, pallor, nausea and vomiting were the most common complaints in our series." They also pointed out that the pattern is not itself a seizure discharge but a sign of a disorder which may have epileptiform manifestation.

It is often correctly said that the electroencephalogram is of little value in most cases of idiopathic grand mal epilepsy, as it is usually unnecessary to obtain such a record to confirm the diagnosis. The case is quite different with paroxysmal disturbances of autonomic or visceral function such as episodic occurrences of pain in various parts of the body. Electroencephalographic examination is even more valuable in behavior disturbances of all types. Such clinical phenomena may be difficult to diagnose, and the electroencephalogram may be the only objective clue to malfunction of the nervous system. Our own material reveals that electroencephalograms obtained in patients with such clinical manifestations, especially children and adolescents, show the 14 and 6 per second positive spikes with striking frequency. Gibbs and Low[4] have said, "In spite of the wide range of symptoms that are associated with this condition, the clinical story is sufficiently characteristic that the physician is often able to predict that 14 and 6 per second spikes will be found in the electroencephalogram."

TABLE 8

COMPARISON OF INCIDENCE OF THE 14 AND 6 PER SECOND POSITIVE SPIKE COMPLEX BETWEEN PSYCHIATRIC PATIENTS AND THE TOTAL NUMBER OF PATIENTS REFERRED FOR ELECTROENCEPHALOGRAPHIC STUDY 1 TO 20 YEARS OF AGE

	Total group	*Psychiatric group*
Number of electroencephalographic records	829	146
Normal records	215	38
Per cent	26	26
Abnormal or borderline records	614	108
Per cent	74	74
Positive spikes	110	34
Per cent of total records	13.3	23.2
Per cent of abnormal or borderline records	18.0	31.4

The urgency of taking sleep records cannot be overemphasized, since the wake record in the great majority of cases is not remarkable. Thus, in a striking number of patients, the presence of this type of electrical pattern may be of diagnostic value. This is of utmost importance when dealing with a young patient who has variously described psychiatric or behavior disturbances – difficulties in school adjustment, disciplinary problems, and the like. In our own series, almost one-third of such patients referred for electroencephalographic study had the positive spike complex

in conjunction with an abnormal or borderline electroencephalogram. It is interesting to note that our figure of 74% abnormal records for this group corresponds closely to that reported by Taterka and Katz[5] in their study of the electroencephalogram in emotionally disturbed children. They found that 78.6% of schizophrenic children and 73.4% of primary behavior problems had abnormal records.

Our records show a high incidence of this electroencephalographic abnormality in comparison with other reported figures. It is significantly higher than the incidence in normal subjects reported in other series. Perhaps the interest we expressed to our colleagues in the electroencephalographic study of patients with vague, ill-defined, possibly epileptiform manifestations and behavior disorders resulted in having an unusually large number of such patients referred to this laboratory.

All our records were obtained by the monopolar technic during sleep – the two conditions most advantageous for evoking this particular pattern. Our patients were unselected, with a generous admixture of children and, of course, a large number of patients who had the clinical manifestations of convulsive disorders.

We are not in a position at the present time to report upon a formal follow-up study of such patients who have been treated with anticonvulsant drugs. Most of them do, however, receive this form of treatment on the basis of their clinical history and the electroencephalographic findings. In many such patients, the family doctor as well as the treating physician has reported dramatic disappearance of the episodic disturbance and improvement in behavior.

It is beyond the confines of this clinical study to comment upon the origin of this type of electrical discharge. Nevertheless, one of our cases may provide a clue to the origin of these complexes. This 10-year-old girl had been having left-sided focal seizures since the age of 17 months. At the age of 1 year, the child's disability was diagnosed as meningitis. After this, she was left with a severe left hemiparesis which, as the child grew, was complicated by extensive atrophy of the entire left side. The patient's convulsize seizures were intractable to medical anticonvulsant therapy, and, because of their focal nature, hemispherectomy was performed (Fig. 5).

At no time before the operation were 14 and 6 per second positive spike complexes noted in her awake or sleep records. The right hemisphere was removed, but the central gray masses were spared. After the operation, positive spike complexes appeared (Fig. 6). It is possible that the sudden appearance of this type of electrical discharge derives from the fact that, before the operation, the cortical discharges overshadowed those arising from deeper structures.

This 14 and 6 per second positive spike pattern has long been thought to originate in the deep midline structures of the brain. Electrically, the pattern is almost always bilaterally synchronous and symmetrical. This suggests a midline point of origin projecting to both hemispheres. Many of the prominent clinical manifestations of epileptic cases – visceral and autonomic disturbances – have been proved to derive from hypothalamic discharges. Stephenson[6] reported finding such electroencephalographic discharges in a patient with a thalamic-hypothalamic neoplasm, and Gibbs and Low[4] reported having seen them in patients shown by pneumoencephalography to have gross lesions involving the thalamus and the hypothalamus.

In general, the 14 and 6 per second positive spike complex is an alteration of the electroencephalogram which correlates well with the presence of one of three clinical conditions – overt clinical convulsions, behavior disturbances, or epileptic equivalents. In the latter two situations, the electroencephalogram is of great value in diagnosis. Sleep records should always be obtained in such cases, and special care taken to look for the 14 and 6 per second positive spike complexes.

SUMMARY AND CONCLUSIONS

The 14 and 6 per second positive spike complex was seen in 6.4% of 2,209 routine electroencephalographic records. This is somewhat higher than usually reported. The pattern was found in 10.5% of all abnormal or borderline records. There was a high incidence of the pattern in the group aged 11 to 20 years, where it accounted for 17.9% of all records and 25.2% of the abnormal records. More than

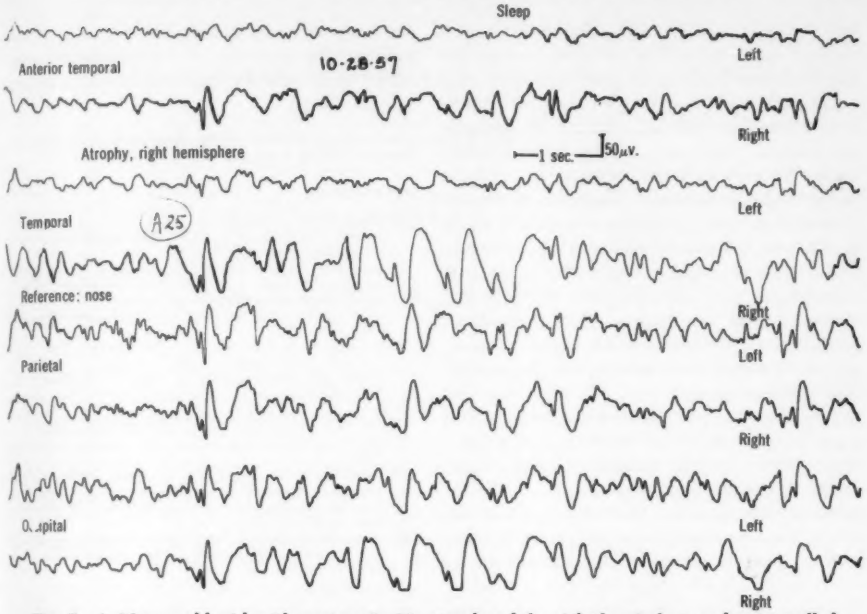

Fig. 5. A 10-year-old girl with postmeningitic atrophy of the right hemisphere and uncontrolled left-sided convulsive seizures. This monopolar recording shows right-sided spike and slow-wave focus.

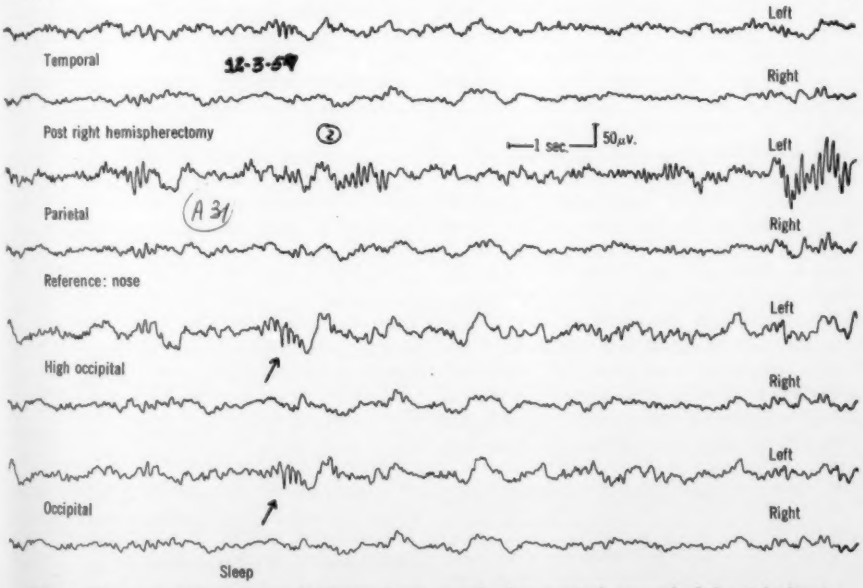

Fig. 6. The same patient shown in Figure 5 one month after surgical removal of the right hemisphere. The monopolar recording reveals a depression of electrical activity over the entire right side and 14 per second positive spikes in the left temporooccipital region.

half of the records with this pattern also showed some other type of electroencephalographic abnormality. Of patients with this abnormality, 42% had had a history of clinical convulsions and 40% had histories of epileptic equivalents, migraine, or behavior disturbances. In over half the patients, no etiologic factor could be detected. Evidence of organic disease of the central nervous system was noted in 20%, and 14% gave a history of head trauma. Comparison of young patients with psychiatric disturbances with an equivalent group of patients referred for routine electroencephalographic study showed a much higher percentage of 14 and 6 per second spike abnormality in the former group.

This electrical pattern seems to be most frequently encountered in children and adolescents whose clinical histories suggest autonomic or visceral manifestations, headache, or behavior disturbances. The importance of obtaining electroencephalographic examination in such patients is stressed. The 14 and 6 per second positive spike complex indicates, in our opinion, the presence of an epileptiform disorder which should be treated with anticonvulsant drugs.

The assistance of Miss Dorothy Henderson, electroencephalograph technician, is gratefully acknowledged.

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Electroencephalographic observations during experimental hyperammonemia

W. P. Wilson, M.D., and Malcolm P. Tyor, M.D.

ELECTROENCEPHALOGRAPHIC studies of hyperammonemia secondary to hepatic failure have demonstrated a gross correlation of blood ammonia levels with changes in the electroencephalogram.[1–5] Friedlander[6] has suggested that rapid deterioration of the electroencephalographic record may occur above a critical level of 200 to 400 μg. of ammonia per 100 cc. of blood. Phillips and associates[1] and Schwartz and associates[7] in a comprehensive study of venous blood chemical changes occurring during hepatic coma found little relationship between blood ammonia levels and clinical changes. No consistent alterations in venous blood *p*H or potassium values were observed. These authors concluded that serial venous ammonia measurements were not precisely correlated with the level of consciousness. Arterial ammonia levels have been reported to be more closely related.[8,9]

With the exception of the work of Marossero and associates[10] all previous studies have been carried out in diseased subjects, many of whom had other metabolic defects accompanying the hepatic disease. The object of this investigation was to determine the effects of elevated blood ammonia levels and associated metabolic defects. In addition, observations on the permeability of the blood-brain barrier to ammonium ion were made.

METHOD

Ammonia was administered to 9 hospitalized males without evidence of hepatic, renal, or central nervous system disease. The age range was 25 to 46 years. With the patient recumbent, 37 to 94 mEq. of 0.155 M ammonium lactate (6 subjects) or ammonium chloride (3 subjects) was infused intravenously over a one-hour period at rates varying between .007 to .018 mEq. per minute per kilogram for the first thirty minutes and .014 to .025 mEq. per minute per kilogram for the next thirty minutes. Blood for analysis was obtained from the brachial artery before infusion, after infusion for thirty minutes and for one hour, and fifteen minutes after discontinuation.

After 4 dogs weighing 10 to 16 kg. were lightly anesthetized with Nembutal, 30 to 55 mEq. of ammonia was infused over a sixty-minute period. Arterial and venous blood samples were obtained before infusion and at fifteen-minute intervals throughout the procedure. Venous blood was obtained from the superior sagittal sinus after trephination of the skull, and arterial blood was taken percutaneously from the femoral artery.

The blood ammonia was measured by a modification of the microdiffusion method of Brown and associates.[11,12] The *p*H of whole blood was measured with a Cambridge Model R *p*H meter equipped with an enclosed glass electrode. Measurements were made at room temperature and corrected to 37° by Rosenthal's factor.[13] The carbon dioxide content of whole blood was determined by the method of Van Slyke and Neill,[14] and the plasma carbon dioxide content was calculated from this value, the *p*H and hemoglobin concentration by the line chart of Van Slyke and Sendroy. The plas-

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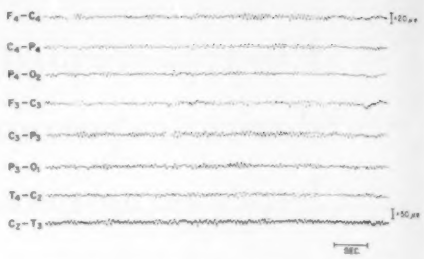
ma carbon dioxide tension was calculated by the Henderson-Hasselbalch equation.[15] Serum potassium and sodium were determined with an internal standard flame photometer.[16] Blood glucose was determined by the method of Nelson.[17]

RESULTS

Human beings. The results of the blood tests are summarized in Table 1. The mean values of ammonia were 506 μg. per cent at thirty minutes and 689 μg. per cent at sixty minutes.



Normal record at sixty minutes (patient F. C.) Blood ammonia = 874 μg. per 100 cc.

TABLE 1

Time of test*	Blood ammonia μg./100 cc. 0	30	60	Post	Potassium mEq./L. 0	30	60	Post	Glucose mm. % 0	30	60	Post	Carbon dioxide tension mm. Hg 0	60
H. L.†	63	583	665	129	4.2	4.4	4.4	3.9	83	91	90	83	43	33
H. D.†	71	357	444	133	4.2	4.3	4.3	4.0	65	70	79	79	50	41
J. D.†	83	420	661	170	4.0	4.8	4.7	4.7	77	78	80	81	49	32
A. G.†	37	614	811	211	4.1	4.6	4.6	4.5	87	92	92	94	43	43
F. H.†‡	71	636	–	–	4.0	4.3	4.2		76	88			44	38
J. C.†	73	223	593	–	4.1	4.3	4.5		80	83	86		44	46
F. C.§	88	660	874	182	3.7	4.7	4.4	4.3	75	85	79	80	46	44
R. M.§	29	479	649	90	3.8	4.0	4.2	4.0	76	83	78	72	42	36
W. B.§	99	583	814	126	4.5	4.6	4.6	4.3	75	76	90	88	40	40
Mean	68	506	689	149	4.07	4.44	4.43	4.24	77.1	82.9	84.3	82.4	†45	42
													§43	40

*0 = Before infusion of ammonia; 30 = after infusion for thirty minutes; 60 = after infusion for sixty minutes; post = fifteen minutes after infusion was discontinued
†Ammonium lactate
‡Vomited
§Ammonium chloride

TABLE 2

ARTERIAL AND CEREBRAL VENOUS AMMONIA LEVELS (μg./100 cc.)

Time of test*	0			15			30			45			60		
	A	V	A-V‡	A	V	A-V	A	V	A-V	A	V	A-V	A	V	A-V
Dog I†	74	80	–6	429	290	139	1129	976	151	2390	1666	724	2836	2137	699
Dog II†	65	63	2	598	403	195	1026	705	321	844	694	150	930	728	202
Dog III†	60	63	–3	1598	529	1069	1480	1110	370	1530	1303	227	1758	1472	286
Dog IV	57	47	10	1261	1103	158	1377	1290	87	1496	1464	33	1503	1462	42
Mean	64	63	1	972	581	391	1253	1020	233	1565	1281	284	1756	1450	306

*Blood was tested before infusion of ammonia (0) and at fifteen-minute intervals throughout the sixty-minute infusion period.
†Immature
‡Arterial-venous difference

Fifteen minutes after infusion was stopped, arterial ammonia levels had dropped precipitously and were approaching the control values.

Arterial potassium concentration increased at thirty minutes when compared to control levels ($d = 0.38$ mEq./L.; $p = < 0.01$). No further change was noted at sixty minutes. No change was noted in sodium values.

Arterial glucose concentration increased significantly at thirty minutes ($d = +5.8$ mg. per cent; $p = < 0.01$). Sixty-minute and post-infusion values did not show a consistent change.

There was no consistent change in the arterial *p*H or carbon dioxide content among subjects given ammonium lactate. Carbon dioxide content of 2 subjects receiving ammonium chloride was decreased at sixty minutes.

Electroencephalographic changes were not produced (see illustration). Nausea occurred in 4 patients. No neurologic changes were observed.

Animals. Ammonia levels in the dogs are listed in Table 2. In all the dogs, marked elevations of arterial blood ammonia levels (930 to 2,836 μg. per cent) were observed. The cerebral arteriovenous ammonia difference increased initially and then declined in 3 animals. In dog I, however, the arteriovenous difference increased progressively, which was attributable to an increasing rate of infusion. In dogs II, III, and IV, the rate of infusion remained fairly stable.

DISCUSSION

Electroencephalographic changes have been demonstrated in man after injection of 26 mEq. of ammonia as a 10% solution of ammonium chloride (4.7 cc.) administered "as rapidly as possible."[10] These alterations consisted of bilaterally synchronous slow waves, which were thought to represent an effect of the ammonium chloride on the reticular system. Studies in dogs supported these findings,[18] demonstrating a suppression of strychnine spikes after injection of ammonium chloride. This suppression was abolished by intercollicular brain-stem transection and by barbiturates. However, an increase in respiratory rate was noted. In addition, the records indicated an increase in respiratory volume which preceded the suppression of the strychnine spikes. Although blood gas levels were not measured, it is conceivable that the altered respiratory rate was accompanied by a respiratory alkalosis, which may be associated with alteration in the electrical activity of the brain. Since others suggest an increased toxicity of ammonia in the presence of alkalosis, their results may be partially explained by a combination of these 2 factors.[19] These observations are in contrast to the earlier findings of Ajmone-Marsan and associates[20] who observed no abnormalities after injection of similar quantities of ammonium ion.

In contrast to the above data, no electroencephalographic changes were observed when ammonia was administered over a more prolonged period. In addition hyperpnea was observed in only 1 patient, who was nauseated at the time of sampling. Though 3 others showed a modest change in CO_2 tension consistent with a respiratory alkalosis, no electroencephalographic changes were observed.

The lack of electroencephalographic changes in normal subjects with arterial ammonia concentrations considerably higher than those observed in most patients with hepatic coma (mean 265 ± 54 for grade III to IV coma)[21] could be related to an impermeability of the blood-brain barrier to ammonium ion in normal subjects. However, the data of Bessman and Bessman[8] and Fazekas and associates[9] do show an uptake of ammonia by the brain in hepatic coma. Our own data derived from the dog experiments show a variable, but at times massive, uptake of ammonia by the brain. As well, the curves of dogs II, III, and IV show an equilibrium phenomenon, larger amounts being taken up early in the experiment. These observations are probably related to the rate of administration of the ammonium ion and possibly to the age of the dog. Similar studies have not been carried out in man.

Bessman[22] has proposed a cerebral biochemical defect in hepatic coma, involving the inhibitory effect of ammonia upon the citric acid cycle. Although ammonium ion is not neurotoxic in the amounts used in these experiments, continuing high levels of ammonia might chronically overload the mechanism that can compensate to a limited extent only by using increasing quantities of γ ketoglutaric acid. This, with time, may interfere with the aerobic

phase of carbohydrate metabolism. The lack of electroencephalographic changes would suggest that Krebs' cycle is not disrupted during the period of our observations. This is supported by the previously observed lack of interference with cerebral oxygen and glucose utilization by ammonium chloride administered at a similar rate and concentration to normal subjects.[23]

The other blood chemical changes caused by infusion of ammonium salts have been discussed in a previous publication.[12] The elevation of arterial glucose and potassium levels may be due to peripheral or hepatic glycogenolysis. It is also possible that the rise in arterial serum potassium results from the gradual displacement of intracellular potassium by ammonium ion. If such occurred in the brain, it would in all likelihood alter cellular function and the electroencephalogram. No data are available to substantiate or refute this notion.

SUMMARY

Electroencephalographic observations were made over a one-hour period in 9 subjects receiving intravenous ammonium salts. In spite of the elevation of the arterial blood ammonia levels to values 2 to 3 times as high as those commonly observed in hepatic coma, no electroencephalographic changes or neurologic signs were observed.

The cerebral uptake of ammonium ion was observed in 4 dogs. Significant arteriovenous differences were observed.

It is concluded that [1] the blood-brain barrier of dogs is freely permeable to ammonium ion and [2] in normal man ammonium ion per se in the quantities used here does not produce electroencephalographic changes when administered over a one-hour period.

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Action of veratrine on human skeletal muscle

With special reference to myasthenia gravis

W. W. Hofmann, M.D.

THE VERATRUM ALKALOIDS, derived from the seeds and rhizomes of certain plants, have been extensively studied during the last seventy to eighty years. Naturally occurring mixtures of these alkaloids, as well as purified derivatives, have interested physiologists the world over because of their pronounced cardiovascular, pulmonary, and skeletal muscle effects; while the latter have been subjected to intense scrutiny in isolated fiber or nerve-muscle preparations from animals, detailed investigations of the veratrine effect on human skeletal muscle have not been reported. These experiments were designed to provide some information on the veratrine effect in human skeletal muscle. The great mass of clinical data regarding the actions of the veratrum alkaloids in hypertension will not be considered here.

Veratridine and cevadine, or a mixture of both (veratrine), are obtained from certain liliaceous plants – chiefly Veratrum viride and Veratrum sabadilla on this continent. Crystalline protoveratrine, jervine, and veratrosine are the main constituents of Veratrum viride, while Veratrum sabadilla yields cevadine, veratridine, and cevine.[1,2] Some of the substances are ester alkaloids which can be hydrolyzed into a basic alkamine and an organic acid. As a rule, the ester alkaloid is a far more powerful pharmacologic agent than the alkamine. In past investigations, the name veratrine has been used to describe the mixture of alkaloids from Veratrum sabadilla and veratrum to describe those from Veratrum viride. As Krayer points out, studies with these crude mixtures may be quite misleading because of the variety of compounds included and the fact that plants from different areas and at different times of year may contain widely differing percentages of the alkaloids. The extensive studies by Jacobs,[3] Craig,[4] and Krayer[5,6] reveal that the alkaloids may be classified to some extent by their chemical and physical properties and also by their dominant pharmacologic effects. Protoveratrine and veratridine exert powerful inotropic effects on the heart, while cevadine probably manifests its most striking action on skeletal muscle. Mixtures of alkaloids, such as found in commercially available veratrum viride, produce widespread physiologic changes, including vasodilation, increase or decrease in respiratory rate, cardiac deceleration, and hypotension. These changes are probably reflex in nature, and some of the effects can be blocked by vagotomy or adequate doses of atropine.[1] The studies of Bezold and Hirt with regard to these cardiopulmonary reflexes, as well as those of Jarisch and Richter, are widely known to physiologists.

The direct inotropic effect of some of the veratrum alkaloids on the failing heart muscle is of considerable interest, and it has been suggested that the alkamines obtained by hydrolysis of the ester alkaloids are rather closely related in chemical structure to the cardiac glycosides,[1] but, while digitalis and veratridine are capable of increasing the work output of the failing mammalian heart, only the latter has been shown to have a marked inotropic effect on skeletal muscle as well. Ouabain seems to lie in an intermediate position because of its moderate effects on both type of muscle.[7]

Veratrine, which contains chiefly cevadine,

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veratridine, and cevine, is the compound which has been used most widely in the study of striated muscle, end-plate, and nerve activity.

The outstanding property of veratrine, as well as of its constituents, is the ability to cause the muscle membrane to depolarize repeatedly after one stimulus.[1,8,9] In addition, the drug produces a sustained, partial depolarization, known as a negative after-potential, in both nerve and muscle.[10,11] This prolonged undirectional current flow could also be regarded simply as a greatly inhibited or slowed repolarization phase,[12] but its characteristics suggest a more active process.[8] During the initial period of repetitive firing, the muscle responds by a tetanus; during the prolonged after-potential, the muscle is in contracture.[13] Propagated spikes are not seen during this latter stage, and the sustained electrotonus will not be apparent in multifiber preparations because of its relatively small amplitude. The over-all result is that the muscle performs more work per stimulus. Whether the efficiency of activity is increased is not known, but it is likely that the consumption of oxygen is increased in proportion to the sustained depolarization. These effects are seen when veratrine is applied to any portion of the muscle membrane. In contrast, acetylcholine, nicotine, and caffeine exhibit their well-known actions only when applied at the end-plate region, and, upon application of these drugs, current flows immediately, indicating partial or complete breakdown of the polarized state.[10] Veratrine, however, produces no alteration of the membrane until at least one impulse, or depolarization, has occurred. The veratrine response can be elicited from the curarized, denervated muscle on direct application of the drug, but the repetitive action potentials may remain localized to the treated segment if curarization is sufficiently complete.

Among the agents reported to block the veratrine response are procaine, eserine,[15,16] and anodal current.[13] Lowering the concentration of extracellular sodium also decreases the veratrine effect, presumably by inducing an hyperpolarized condition at the membrane[17] so that the negative after-potential is not of sufficient height to generate propagated spikes. Eserine, procaine, and procaine amide are said to produce a decrease in the tetanus and contracture phases as well as in the force of contraction after veratrine,[16] but the mechanism is not clear. Blockage of potassium efflux and inhibition of sodium[18] influx have been attributed to procaine and procaine amide, but preliminary studies in this laboratory indicate that veratridine easily overcomes the progressive block induced by procaine amide and that previous antagonism suggested between these drugs may simply have been a matter of dosage. The response to anodal current is the result of complete membrane polarization so that veratrine cannot exert its usual effect.

Veratrine does not alter neuromuscular transmission in any way. The output of the transmitter substance, acetylcholine, is not increased; the alkaloid has little, if any, anticholinesterase activity;[1] and the muscle sensitivity to acetylcholine is not increased. The depolarization induced by the normal nerve impulse is not temporally altered, and no blocking effects are seen unless very large doses are used.[8] While veratrine is capable of producing exactly similar electrical changes in nerve, the responses seen in muscle are not the result of repetitive nerve discharges since they occur on direct application of the alkaloid to the muscle.

Pharmacologically and clinically, part of the veratrine response is quite similar to true myotonia. This fact plus a consideration of myasthenia gravis, in which condition the muscle membrane seems to resist depolarization, led to the idea that the veratrine response in human subjects, especially those suffering from faulty neuromuscular transmission, might be of considerable interest. A similar idea, unknown to the author at the time of these experiments, was proposed in the German literature in 1934, but the report has not been widely publicized.[20]

MATERIAL AND METHODS

Included in this study were 25 healthy subjects used as controls and 4 patients with well-defined, generalized myasthenia gravis. The technic consisted in percutaneous application of maximal or supramaximal rectangular pulses to the ulnar nerve above the elbow and recording the evoked muscle action potentials from the abductor of the fifth finger (Fig. 1). The force of contraction was recorded by

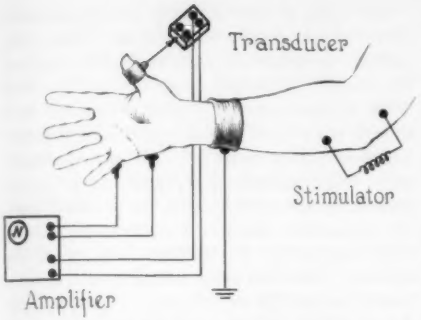

Fig. 1. Amplification of evoked potentials and mechanical responses was accomplished by using a Grass Model III electroencephalograph with ink writers. The action potentials were simultaneously observed and sometimes photographed on a single beam oscilloscope.

means of a strain gauge attached to the thumb in such a manner as to be activated by contractions of the adductor of the thumb. Since the mechanical response was fed into a condenser-coupled amplifier, only the initial deflection was indicative of the force of contraction. While force and electrical measurements were made from different muscles, innervation of both is from the stimulated nerve. The muscle action potentials were recorded from the skin and represented the integrated discharge of fibers between the electrodes. The frequency of stimulation varied from 1 to 25 per second with shocks of 0.1 to 0.6 msec., duration. Short trains of shocks as well as single pulses at one-second intervals were used to study drug effects. In the first experiments, the stimulator was not providing supramaximal shocks, but, from these records, only clear-cut and drastic changes after drug administration were included. Recording was by means of a Grass Model III EEG and single beam oscilloscope.

Arterial injections were made through an indwelling No. 18 Cournand needle inserted into the brachial artery at the elbow, and venous blood was sampled from a needle remaining in the antecubital vein. All injections were made up to a volume of 2 cc. The arterial supply was occluded with a blood pressure cuff during injection, and, after lowering the pressure to allow the test agent to be washed into the arm, the cuff was inflated partially to occlude venous return to the systemic circuit for five minutes.

The solutions of veratrine, veratridine, and cevadine were generally made up a few hours before use, and, since these solutions are destroyed by boiling, sterilization was achieved through pressure filtration. The acetylcholine, d-tubocurarine, and neostigmine solutions were made up at the time of experiment. The *p*H of the veratrine solutions was adjusted to approximately 7.4.

All control patients were examined neurologically and found to be free of lower motor neuron or muscle defects clinically.

In the experiments to be described, either veratridine, cevadine, or a mixture of both in about equal proportions (veratrine) was used.

The first studies were designed to test the effect of the veratrum alkaloids alone, in doses of 20 to 100 μg., on the evoked potentials of healthy subjects. At the rate of 25 shocks per second, there was some tendency for decay of potentials, averaging about 15% in some subjects without medication. This was attributed to increasing tissue impedance during the train of shocks and was corrected in later experiments by reducing the skin resistance to less than 1,000 ohms and increasing the current output from the stimulator.

The effects of intraarterial veratrine are shown in Figure 2. The size of the integrated action potentials and, therefore, the number and amplitude of the responding muscle units were not significantly altered. In about one-third of the patients, veratrine produced an enduring asynchronous discharge outlasting each train of 4 or 6 shocks by several seconds. Sometimes, repetitive discharge was seen after single shocks (Fig. 2). This same type of discharge was also seen in some patients without medication. The prolonged partial depolarization, or negative after-potential, presumably evoked by the alkaloid, was not seen at the surface because of the short time constant of the condenser-coupled amplifier and the tendency of different muscle units to fire somewhat asynchronously. Except for the repetitive after-discharge sometimes seen, veratrine had little or no effect on action potentials that were evoked either in trains or singly at one-second intervals.

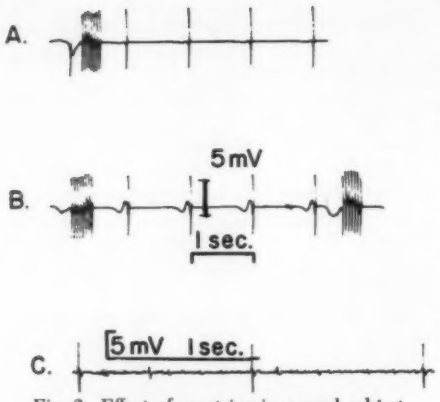

Fig. 2. Effect of veratrine in normal subject *(A)* Evoked potentials in normal subjects before medication. *(B)* Same patient one minute after intraarterial injection of 100 γ of veratrine. The evoked potentials are not changed. No after-discharge was noted in this record. *(C)* Normal subject. Enduring repetitive discharge after injection of 100 γ of veratrine. This phase of the drug effect was observed in about one-third of cases.

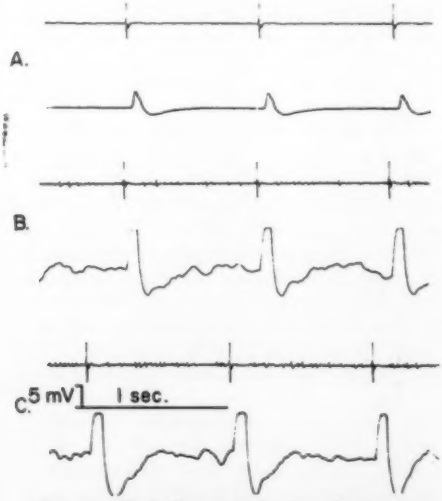

Fig. 3. Evoked potentials *(top line)* and force of contraction *(lower line)*. *(A)* Records before medication — single shocks. *(B)* Records two minutes after injection of 80 γ of veratrine intraarterially. *(C)* Showing duration of veratrine effect. Record taken twelve minutes after injection of veratrine. Time and voltage scale apply to all records.

The force of contraction in healthy subjects, however, was significantly increased after veratridine, veratrine, or cevadine. The record of the muscle shortening indicated as much as 200% increase in one subject (Fig. 3), even though the stimuli before injection of the alkaloid had clearly been found to be supramaximal. When sustained repetitive activity was seen in the electromyogram, the record of muscle contraction mirrored the electrical activity, with continuing fluctuations long after the stimulus; the increased twitch tension usually lasted ten to fifteen minutes (Fig. 3). With the recording technic used, it was not possible to obtain accurate measurements of the duration of the augmented muscle twitch, but, on clinical examination of these patients after administration of veratrine, the delay in relaxation observed closely resembled true myotonia. In one patient, tapping the muscles of the thenar eminence shortly after veratrine administration produced a rather prolonged shortening resembling percussion myotonia.[21] Sustained repetitive discharge was not seen at the surface in all patients showing the myotonic response, however, and it is assumed that a good portion of the heightened mechanical activity originated in the contracture phase. Thus, the similarity to true myotonia is incomplete.

The veratrum alkaloids did not seem to shorten the normal delay time between stimulus and muscle shortening, and careful measurement of the evoked potentials indicated that, although the force of contraction might be greatly increased after both single and multiple shocks, neuromuscular transmission remained unchanged. In fact, no recruitment was observed after veratrine administration, even when submaximal stimuli were given. The force response was, nevertheless, increased.

Potassium determinations were carried out on 8 healthy and 2 myasthenic subjects. The arteriovenous difference at rest indicated a slight net leakage of potassium from muscles before stimulation or injection of medication in 4 of the normal subjects and 1 myasthenic patient; the resting venous potassium was the same as arterial in the remaining subjects studied. The differences in both directions are small, averaging only 0.1 to 0.4 mEq. per

liter, but, as other investigators have indicated, these differences in extracellular potassium may be physiologically quite significant.[22] After a train of shocks lasting thirty seconds, all but 1 of the healthy subjects showed a loss of potassium of 0.1 to 1.1 mEq. per liter, averaging 0.4 mEq. per liter. No measurable loss of potassium from the muscles was shown in 1 patient with myasthenia gravis; the other lost 0.2 mEq. per liter.

The greatest increase of venous potassium from the stimulated arm was observed in a patient with mild myxedema. This patient was the only one showing a slight uptake of potassium at rest, arterial being 4.0 and venous 3.9 mEq. per liter. She also showed a delayed relaxation after the stretch reflexes were elicited at the knee – the myotonia of hypothyroidism.

After administration of veratrine in doses of 40 to 100 μg., the muscles in 2 patients seemed to lose more potassium in response to a second, long train of shocks of thirty seconds' duration. Sufficient time, fifteen minutes, was allowed between the two long trains of shocks for the leakage of potassium from the first train to have been carried away by the venous blood. The elevation of venous potassium beyond that recorded for the first train of shocks was again very small in the 2 patients, being 0.1 and 0.5 mEq. per liter, respectively. In the 2 other patients so studied, the potassium remained unchanged in the first, dropping to 0.3 mEq. per liter in the second. In 2 patients with myasthenia gravis, 1, with a severe case, failed to show any potassium leakage even after veratridine and the other, with a mild myasthenia, showed a normal loss.

The action of veratridine or veratrine relative to acetylcholine was next studied. Control potentials were measured before and after intraarterial administration of acetylcholine in doses of 0.2 to 5.0 mg. The prompt depolarizing effect of acetylcholine was usually obtained with doses of 0.4 mg., but the sensitivity of different individuals to this quaternary ammonium compound was found to vary widely. Then, veratridine or veratrine was given and the prompt depression of potentials again measured. The nicotinic effect of the injected acetylcholine was apparently not enhanced or depressed by administration of veratridine, but

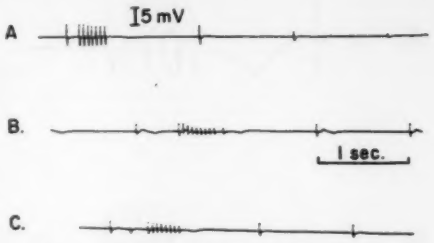

Fig. 4. Failure of large dose of veratrine to alter depolarizing block. Single and repetitive stimulation. *(A)* Evoked potentials before and during prompt depression induced by 5 mg. of acetylcholine intraarterially. The prompt depression was too brief to study concurrent effects of veratrine. *(B)* Seven minutes after injection of acetylcholine. Delayed acetylcholine block. *(C)* Eight minutes after acetylcholine and thirty seconds after 80 γ of veratrine. No significant change in potentials.

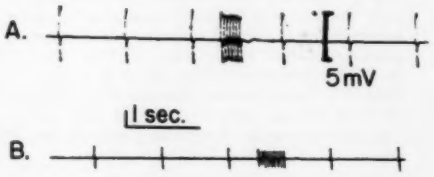

Fig. 5. Failure of previously administered veratridine to inhibit depolarization block. *(A)* Record after 3 injections of 40 γ veratridine twenty, ten, and five minutes before. Single and repetitive stimulation. *(B)* Prompt depressant effects of 5 mg. acetylcholine ten seconds after injection. Seven minutes after last dose of veratridine.

the brevity of the prompt blocking action of acetylcholine made accurate measurements difficult. The late depressant effects of acetylcholine were noted several minutes after injection. This delayed depression also assumed in most normal subjects the characteristics usually associated with a depolarizing block and was not changed by veratridine or veratrine (Fig. 4). Acetylcholine itself, in some subjects, initiated a very few repetitive spikes during the phase of prompt depression, but this phase of its activity always was accompanied by partial or complete paralysis, that is, no movement was produced by the shocks for a short period. Prior administration of veratridine did not

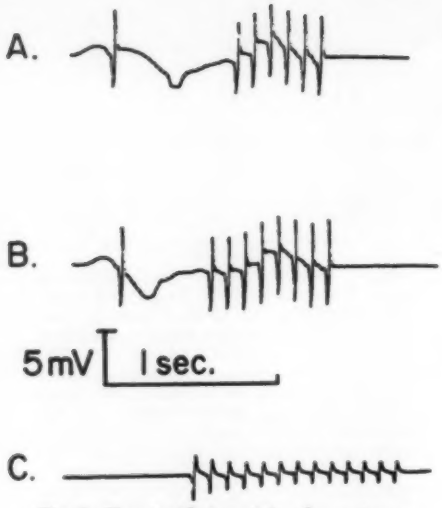

Fig. 6. Showing that veratrine does not prevent the competitive block produced by d-tubocurarine in normal subjects. *(A)* Evoked potentials before medication. *(B)* Forty seconds after intraarterial injection of 20 γ veratrine. *(C)* Three minutes after the above dose of veratrine and sixty-five seconds after 0.3 mg. d-tubocurarine. Electrical potentials decay as if curare alone had been given.

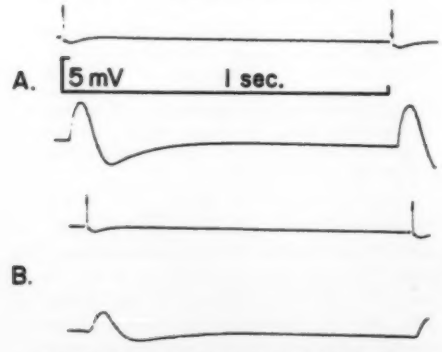

Fig. 7. Subsequent injection of d-tubocurarine after veratrine effect established. *(A)* Evoked potentials *(top line)* and force of contraction *(bottom line)* three minutes after injection of 80 γ veratrine. Force of contraction still considerably greater than before veratrine. *(B)* Five minutes after above dose of veratrine and one minute after 0.3 mg. d-tubocurarine. Both action potentials and force of contraction decreased, suggesting that curare blocks both the tetanic and contracture phase of the veratrine response.

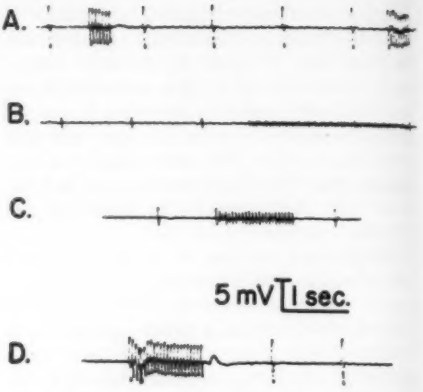

Fig. 8. Comparing the action of injected acetylcholine and veratrine on the block induced by curare. *(A)* Evoked potentials before injection — trains and single shocks. *(B)* Two minutes and forty seconds after 0.3 mg. d-tubocurarine. *(C)* Five minutes after above dose of d-tubocurarine and two and one-half minutes after 80γ veratrine. Note minimal restorative effect of action potentials. *(D)* Ten minutes after above dose of d-tubocurarine and one minute after 2.5 mg. acetylcholine, showing prompt decurarizing effect of acetylcholine in contrast to *C*.

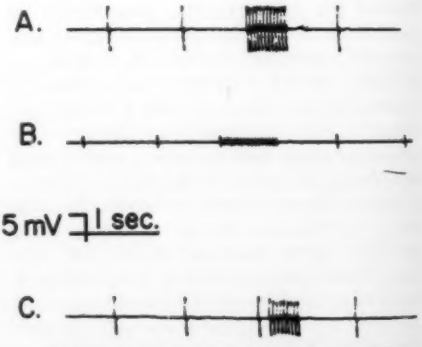

Fig. 9. Effect of mixture of veratrine and d-tubocurarine. *(A)* Evoked potentials prior to injection. *(B)* Three and one-half minutes after injection of mixture of 0.3 mg. d-tubocurarine and 80 γ veratrine. Mixture acts as if curare had been given alone. *(C)* Five minutes after above injection and twenty-five seconds after 2.5 mg. of acetylcholine, showing prompt decurarizing effect of the latter, while veratrine was ineffective.

change the characteristics of the response to acetylcholine given one to five minutes later (Fig. 5).

The effects of the veratrum alkaloids in relation to d-tubocurarine were next investigated. Curare was given in doses of 0.3 to 0.6 mg. in single or repeated doses as necessary to produce paralysis of both spontaneous and electrically evoked contractions. In confirmation of previous reports,[23] these experiments showed clearly that successive doses of curare produce less block. Prior administration of veratrine, in doses of 20 to 100 μg., failed entirely to prevent the decay in potentials (competitive block) or drop in force, produced by curare (Figs. 6 and 7). In addition, administration of veratridine after the curare block was well developed led to no significant increase in either the force of contraction or the amplitude of the evoked potentials (Fig. 8). Repeated trains of shocks produced the usual decurarizing effect, and injected acetylcholine showed sustained and pronounced anticurare activity (Fig. 8). A mixture of 0.3 mg. of d-tubocurarine and 80 gamma of veratridine acted as if the curare alone had been given (Fig. 9), and the response to subsequent acetylcholine was unchanged.

Posttetanic potentiation, the increase in contractile force which develops after a train of shocks, was compared to the effects of intra-arterial veratrine. Botelho[24] has shown that significant potentiation develops in man without any change in the size or shape of the integrated action potential recorded through the skin after a train of shocks. Since this exaggerated mechanical response is similar to that obtained with veratrine, the two phenomena were studied consecutively in several patients. After attaining supramaximal stimulus strength, the action potentials and force of contraction were carefully measured. Then, a ten-second train of shocks was given and the measurements repeated. In agreement with Botelho, a significant rise in the force of contraction to single shocks was noted after the train; this potentiation lasted for several minutes. The action potentials remained unchanged, indicating that no facilitation of neuromuscular transmission had occured.[25]

Veratrine or veratridine, in doses from 80 to 100 μg., was injected after the muscles had returned to the resting state. These drugs produced a much greater potentiation than a tetanus alone, and the effects lasted much longer — up to fifteen minutes (Fig. 10). Some spontaneous after-discharge was noted, but the action potentials remained as before. Some of the re-

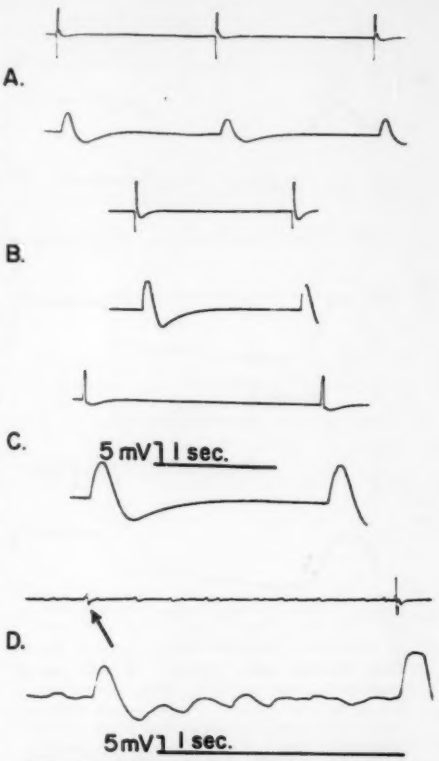

Fig. 10. Comparing posttetanic potentiation with veratrine effect. *(A)* Evoked potentials *(top line)* and force of contraction *(bottom line)* in normal subject. *(B)* Ten seconds after five-second train of supramaximal shocks, showing posttetanic potentiation. *(C)* Same subject thirty minutes later and fifty seconds after injection of 80 γ veratrine, showing augmented mechanical response while action potentials become monophasic. *(D)* Showing that spontaneous discharge after veratrine is also capable of eliciting forceful contraction. Same subject as in *A* and *B*, different time scale. Compare force of contraction elicited by small number of fibers after veratrine *(arrow)* with supramaximal resting response in *A*.

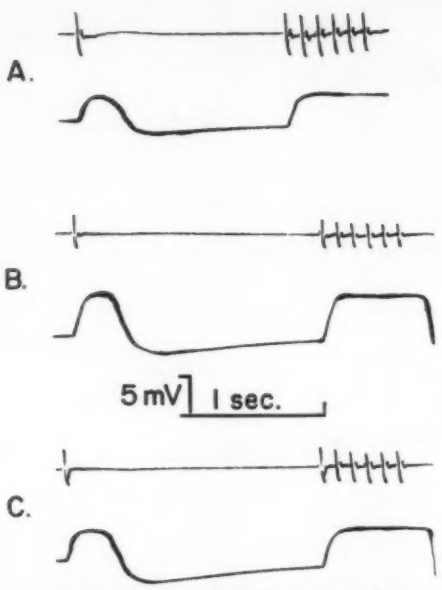

Fig. 11. Effect of neostigmine in normal subject. *(A)* Evoked potentials *(top)* and force of contraction *(bottom)* before injection. *(B)* Forty seconds after injection of 0.25 mg. neostigmine intraarterially. Strain gauge record slightly retouched. Single action potentials show some decrease, and train shows progressive decay. Force of contraction, however, is increased with both. *(C)* Three minutes after injection. Some depression of action potentials still present, but force of contraction still slightly increased. Number and amplitude of discharging units beneath electrode need not reflect mechanical response.

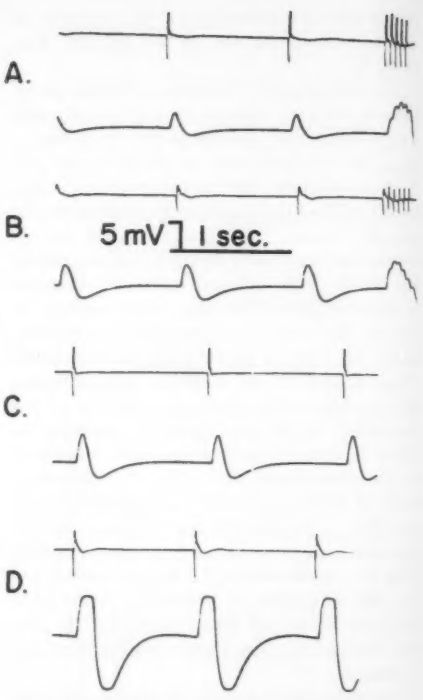

Fig. 12. Comparison of neostigmine and veratrine in normal subjects. *(A)* Evoked potentials *(top)* and mechanical response *(bottom)* with supramaximal stimuli. *(B)* Twenty seconds after intraarterial injection of 0.25 mg. neostigmine. Action potentials clearly blocked while force of contraction increases slightly. *(C)* One and one-half minutes after neostigmine injection. Action potentials restored, force still increased. *(D)* Six minutes after neostigmine and one minute after 80 γ veratrine. Action potentials remain as before while force of contraction greatly augmented.

petitive discharges alone were capable of producing a stronger contraction than that previously elicited by supramaximal stimulation of all the fibers (Fig. 10). Not all patients showed spontaneous after-discharge, however, suggesting that repetitive activity at the muscle membrane – the so-called tetanic phase – is not essential to this inotropic action of the Veratrum alkaloids.

Since neostigmine is reported to have some direct action on the cell membrane as well as its anticholinesterase activity,[26] the effects of this drug were compared to those of veratrine and veratridine. The usual phenomenon observed in normal subjects after the administration of neostigmine was a curare-like progressive decay in evoked action potentials during a train of shocks (Fig. 11). This decay during tetanus was striking and was accompanied in one case by a slightly decreased force of contraction and in the remainder by a moderate increase in force, even while the evoked potentials were waning (Fig. 12). The

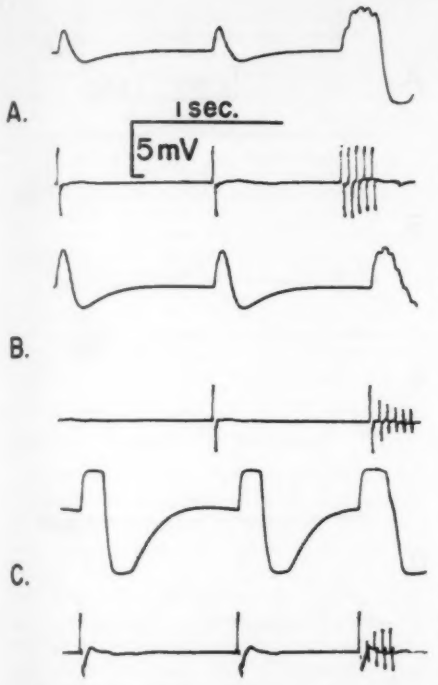

Fig. 13. Comparison of neostigmine and veratrine. Block induced by neostigmine does not impede inotropic effect of veratrine. *(A)* Force of contraction *(top)* and evoked potentials *(bottom)*. Supramaximal stimuli before injection. *(B)* Fifty-five seconds after 0.25 mg. neostigmine. Single potentials slightly decreased while train decays markedly. Force of contraction with single shocks increased nevertheless. *(C)* Three minutes after neostigmine and one and one-third minutes after 100 γ veratridine. Though neostigmine block is still present, force of contraction exceeds limits of writing device.

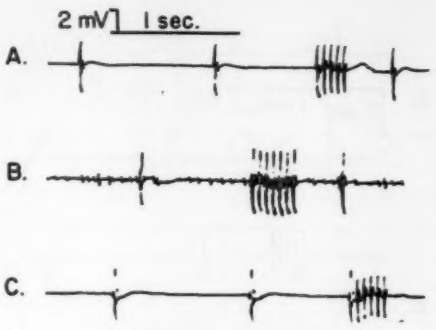

Fig. 14. Restoration of action potentials in myasthenia gravis. *(A)* Evoked action potentials in patient with myasthenia gravis. Slight decay during train of supramaximal stimuli. *(B)* Sixty seconds after intraarterial injection of 0.25 mg. of neostigmine. Note after-discharge. *(C)* Two and one-third minutes after neostigmine. Potentials have returned to resting state.

potentials recorded with single shocks also decreased in the healthy subject for about one minute after 0.25-mg. doses of neostigmine. The force of contraction was increased slightly, however, even in healthy subjects undergoing proved supramaximal stimulation (Fig. 13). The effect on both single and trains of evoked potentials took a relatively long time to develop – from twenty to thirty seconds. The duration of the muscle shortening seemed to be increased in normal subjects given neostigmine, but this suggestion may be questioned in view of the recording devices used. Veratrine induced a much greater force of contraction in normal muscle than did neostigmine (Figs. 12 and 13).

In one patient with well-defined, moderately severe myasthenia gravis, the neostigmine also produced a progressive decay in potentials for a short period of approximately twenty seconds after injection, but this was followed by the usual increase in electrical activity above that evoked before the administration of the drug (Fig. 14). The usual effect of neostigmine in myasthenic patients was to increase the action potentials significantly and the force of contraction only slightly. The duration of the repair of action potentials was short, lasting for an average of only two minutes. The outstanding feature of the neostigmine response in these myasthenic patients was its comparative brevity.

While neostigmine produced a slight increase in force of contraction in normal subjects and in the myasthenic patient, the veratrum alkaloids used produced a more prolonged and forceful mechanical response in both situations without augmenting the elec-

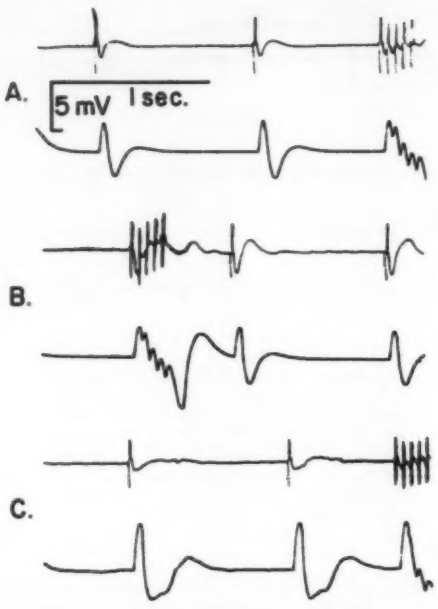

Fig. 15. Myasthenic subject: last dose of prostigmine, 15 mg., six hours before. Comparison of neostigmine and veratrine. *(A)* Evoked potentials *(top)* and force of contraction *(bottom)*. Slight decay in train of potentials at 25 per second. *(B)* Sixty seconds after 0.25 mg. neostigmine intraarterially. Action potentials slightly retouched. Tendency of action potentials to decay restored. Force of contraction essentially unchanged. *(C)* Six minutes after neostigmine and one and one-half minutes after 80 γ of veratrine. Action potentials slightly lower while force of contraction markedly improved.

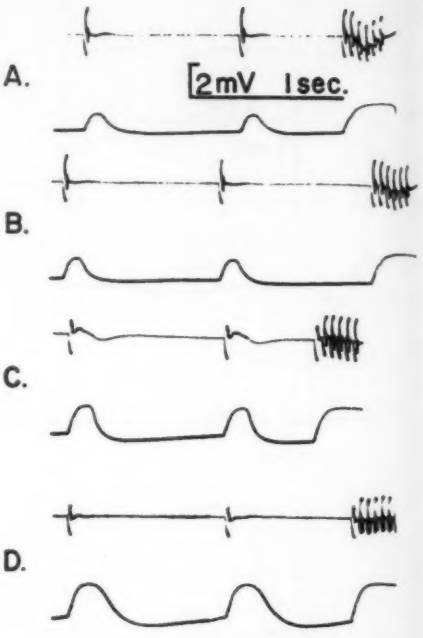

Fig. 16. Myasthenic subject: last dose of Mestinon, 60 mg., eighteen hours before. *(A)* Evoked potentials *(top)* and force of contraction *(bottom)*. Note decay in action potentials during train of shocks. *(B)* Fifteen seconds after 0.25 mg. neostigmine. Slight increase in force of contraction already evident, while action potentials essentially unchanged. *(C)* One and one-half minutes after neostigmine, 0.25 mg. intraarterially. Single action potentials actually appear blocked slightly, but train of potentials now shows no decay. Force of contraction further increased. This record shows the maximum mechanical response ever elicited in this patient with neostigmine. *(D)* Five minutes after neostigmine and one and one-fourth minutes after 100 γ of veratrine. Mechanical response significantly greater than maximum neostigmine response, and muscle twitches seem prolonged despite decay in action potentials. The late block in action potentials at *D* may represent the late depressant effect of the acetylcholine accumulated during the neostigmine action or may be the result of myasthenic fatigue in this patient after several hundred stimuli.

trical response in either (Fig. 15). Furthermore, when neostigmine repaired the action potentials, that is, restored activity of the transmitter substance, in myasthenic patients, subsequent injection of veratrine did not improve the action potentials but simultaneously increased the force of contraction by perhaps 50% (Fig. 16). After the neostigmine-induced rise in action potentials had fallen again to the resting level, the increased force response due to veratrine persisted unchanged for several minutes (Fig. 17).

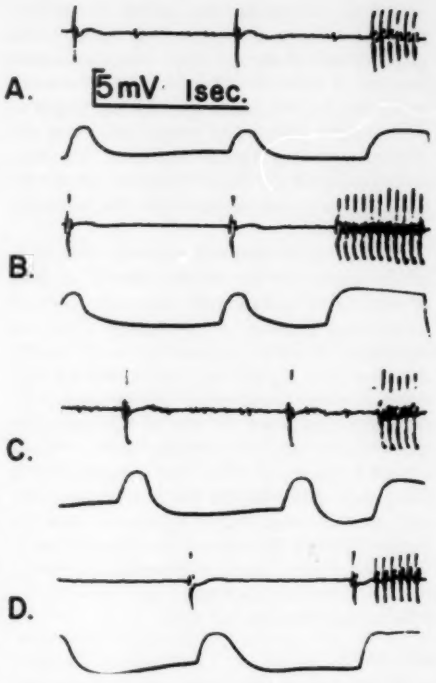

Fig. 17. Myasthenic patient. Comparison of veratrine and neostigmine. *(A)* Evoked potentials *(top)* and force of contraction *(bottom)*. Note progressive decay with train of shocks and spontaneous after-discharge even in myasthenic patient. Last dose of oral neostigmine twenty-four hours before test. *(B)* Two minutes after intraarterial injection of 0.25 mg. neostigmine. Action potentials restored, force of contraction slightly improved. *(C)* Three minutes after neostigmine and twenty seconds after 100 γ veratrine. Action potentials still improved but began to decay immediately after this record. Force of contraction now greater than maximum response to neostigmine. *(D)* Four minutes after veratrine. Action potentials have been at resting level for several minutes, but increased mechanical response to veratrine persists.

RESULTS

These experiments show conclusively that certain of the veratrum alkaloids are capable of exerting a powerful inotropic effect on human muscle, that this effect is evident in patients suffering from myasthenia gravis, and that, in the latter condition, the improvement in muscle strength is of far greater amplitude and duration than that obtained with a standard anticholinesterase drug when injected intraarterially.

Because of the marked improvement in muscle strength seen in myasthenia gravis after injection of veratrine into the artery of one extremity, experiments were conducted with one myasthenic patient to evaluate the activity of the alkaloid given systemically. The patient's usual six hourly dose of Mestinon was stopped and the experiments were started as nearly as possible in the basal state. The results were moderately encouraging. The bilateral ptosis, present before the infusion, cleared nicely; grip strength, which had declined precipitously, increased over a series of trials; and the patient's ability to raise her head repeatedly from the pillow also increased. These apparent benefits lasted unchanged for about five hours after a total dose of 160 μg. of veratridine. The test was performed at 11:00 A.M., after the patient had been without her usual medication for approximately eighteen hours. Although the elimination of medication made it difficult for the patient to swallow and chew her breakfast before the test, she was able to eat lunch without dysphagia and had no further difficulty with eating until supper time on the test day. She stated that she felt as well or better than if she had taken 2 Mestinon tablets, and she added that her mild diplopia had cleared. By the next morning, all her myasthenic symptoms had returned, even though she had taken 120 mg. of Mestinon at 2:00 A.M.

On the second day, the test was repeated; a total of 150 cc. of veratrine in doses of 4 μg. per cubic centimeter was given. Frequent electrocardiographic samples were obtained and showed no changes. Again, the ptosis cleared, the face became more mobile so that the patient could purse her lips, and the grip strength increased. The patient was able to elevate her head a greater number of times. On this occasion, the effects of the drug were less prolonged and the patient had some dysphagia requiring Mestinon about one hour after the veratridine infusion had been stopped.

In order to be certain that the veratrine response in the muscle of the myasthenic patient

would not antagonize the effects of anticholinesterase compounds, Tensilon, 12 mg., was given intravenously one hour after the second infusion of veratridine was stopped. The maximum effect of the latter alkaloid had begun to wane, slight ptosis had reappeared, and the grip strength was slightly decreased. The Tensilon produced its usual transitory effect, decreasing the ptosis significantly. No fasciculations were seen.

Because of the patient's extreme willingness to cooperate and the relative brevity of drug effects on the second trial, she was given an intravenous placebo of physiologic saline on the third day. The preparations were exactly the same, and the patient's belief that she was again receiving veratridine was evidenced by her statement, after 50 cc. of infusion, that she thought she was getting better. When coaxed to maximum effort, she responded until completely exhausted on the head raising and grip tests but there was a significant decay in muscle strength throughout the entire infusion. The most obvious findings were that the ptosis remained entirely unchanged and she was totally unable to purse her lips.

DISCUSSION

The results of these experiments indicate that modification of postjunctional events in human skeletal muscle may lead to quite as dramatic changes in the force output of the muscles as does alteration in the preservation or destruction rate of the transmitter substance. The findings also suggest strongly that the integrated action potential recorded from the skin over a muscle cannot provide information about the enduring states of partial depolarization, or delayed repolarization, which initiate states of local or generalized muscle contracture and are quite capable of altering the work done by that muscle.[27] The discrepancies noted by others between electrical and mechanical measurements of human muscle function are again brought into focus.[28] Electromyography with needles will also fail to give a complete picture of junctional and postjunctional events.

The studies of the effect of veratrine, veratridine, and cevadine on evoked potentials without treatment with other drugs indicate that these agents do not facilitate neuromuscular transmission and only rarely block it in the doses used. The experiments with injected acetylcholine show that these veratrum alkaloids neither reverse the paralytic (nicotinic) effect of the former nor enhance it as do the cholinesterase inhibitors. The absence of any potentiation of the depolarizing block induced by acetylcholine argues against the conception that veratrine has significant anticholinesterase activity.[29] The lack of any signs of progressive decay in action potentials after veratrine also indicates that this alkaloid is incapable of competing with acetylcholine for receptor sites at the end plate. The repetitive after-discharge seen in some of the normal subjects given veratrine was not appreciably altered by prior injections of acetylcholine, and it is surmised, therefore, that this tetanic phase of the veratrine response is not dependent upon excesses of the normal transmitter substance.

Muscular contractures can certainly occur even when no current flows across the membrane,[30] but since single fiber experiments with veratrine have all shown a prolonged negative after-potential and since this current seems perfectly able to induce muscle shortening, it is assumed that the increases of contractile force measured here after veratrine are the result of this delayed repolarization phase. Clear evidence of the tetanic phase of the veratrine response was not consistently observed, even on the simultaneous oscilloscope recordings.

The contracture phase of the veratrine response will, of course, be impossible to evaluate in human beings until the single muscle fiber can be impaled with a microelectrode which will not break off when the muscle responds to the drug. The increases in contractile force seen in these experiments after repetitive stimulation alone was used (posttetanic potentiation) may reflect a sort of contracture related to the treppe phenomenon in cardiac muscle.[31] Veratrine seems to augment the contracture response in human beings.

The experiments with d-tubocurarine show clearly that veratrine has no decurarizing effect in the doses used. This finding is not wholly surprising since veratrine itself causes no current to flow at the end plate or other portions of the membrane (does not depolarize the membrane) and can only exert its effect after at least one impulse has passed.[8] The

competitive block induced by the curare leaves only a few end plates responsive to the emission of acetylcholine. This small number of fibers is not capable of exerting much force or producing normal electrical activity. The inability of veratrine to produce its characteristic effect without previous depolarization of the membrane suggests that the alkaloid may have to penetrate into the cell. Blocking of the carrier mechanism might inhibit such entry. Failure of the alkaloids to decurarize indicates that they do not enhance acetylcholine production by the nerve.

A comparison between the effects of intra-arterial neostigmine and veratrine in both normal and myasthenic subjects reveals that the two compounds produce some rather similar effects. Neostigmine is usually thought of as an anticholinesterase compound, with efficacy stemming from its preservation of acetylcholine, but these experiments suggest that it also has a significant effect on the muscle membrane itself, as does veratrine. In the myasthenic patient whose transmitter substance seems to be blocked, neostigmine has produced a sustained increase in evoked muscle shortening without increasing the number or amplitude of discharging muscle units. Furthermore, in normal subjects, neostigmine was quite capable of producing an increased mechanical response while neuromuscular transmission, as judged by the simultaneously recorded integrated action potentials, was decreased or partially blocked by the drug (Fig. 12). Veratrine, veratridine, and cevadine always evoked a much greater response, however. These effects of neostigmine might easily be attributed to an excess of acetylcholine, except that such an excess of the normal transmitter in the myasthenic patient should certainly increase the action potentials and any excess of acetylcholine in the supramaximally stimulated normal muscle leads to a prompt paralysis of some units. The latter mechanical effect was not observed in healthy subjects, and, as shown above, an improvement in muscle strength in the myasthenic patients was not necessarily dependent upon changes in evoked action potentials.

It seems reasonable to infer, therefore, that neostigmine possesses a dual action and that neuromuscular transmission, as measured in the usual fashion, is not a reliable indication of the pharmacologic activity or efficacy of the drug. There can be no question that the cholinesterase inhibitors restore the activity of muscle, the receptor substance of which is competitively blocked, but the obvious failures with the most modern of these drugs in some cases and the increasing drug resistance of some myasthenic patients during chronic therapy suggest that membrane functions, as well as neuromuscular transmission, may be faulty. The inadequacy of neostigmine in restoring ion conductance at the membrane might be attributed to the relative brevity of the action. While some observers have inferred from measurements of evoked action potentials that neostigmine does not have a direct effect on the muscle,[23] these experiments reveal the risk of drawing such conclusions from the electrical activity alone. Though the drug seems to be able to induce direct membrane changes in both normal and myasthenic subjects, the veratrum alkaloids are much more effective in this regard.

The significant increase in contractile force evoked by veratridine in the myasthenic patients stands against the concept that the weakness of myasthenia gravis results entirely from the activity of a curare-like substance. Even though many investigators have stressed the similarity of myasthenia to partial curarization and it has been clearly shown[25] that the muscle membrane in the former reacts as if it were competitively blocked, the veratrine effect is certainly not blocked and the similarity to curarization fails at least partially.

The few potassium studies done to date are inconclusive at best. Because of previous reports that veratrine[12,32] and other steroids, such as digitalis,[33] prompted a net efflux of potassium from the muscle cell, it was thought that cation studies might shed new light on the action of the former in human beings. A great many more determinations will be necessary to make the data meaningful.

A leakage of muscle potassium with veratridine greater than that obtained with a train of shocks alone occurred in only 2 of the 4 patients so studied. Perhaps more significant was the fact that the patient with severe myasthenia failed to liberate intracellular potassium after any stimulus.

The striking mechanical events after administration of veratrine or veratridine to the myasthenic patient may deserve some consideration. It will be evident that neuromuscular transmission, as judged from the evoked integrated action potential, is defective in myasthenia, but it is also clear that the mechanical response of the myasthenic muscle cannot be judged by the action potential and, in fact, may vary quite independently. Whether an agent improves or restores the amplitude of propagated action potentials need not be the sole criterion of the drug's efficacy in repairing the weakness associated with the disease.

The normal stimulus to muscle activity in human beings seems to produce chiefly a form of tetanus with recruitment as the essential variable in the force of the response, but, while contracture may thus be a rather unphysiologic mode of activity, these experiments show that it can certainly overcome weakness. In fact, what serves to initiate a propagated membrane response may not be affected by the same agents or competitors as those acting on a nonpropagated muscle shortening (contracture), and it seems reasonable to assume that the complete remedy for successive failing of a voluntary muscle might include both agents facilitating neuromuscular transmission with those sustaining partial depolarization of the membrane.

If the apparent competitive (nondepolarizing) type of block seen in myasthenia is in any way related to the ratio of intra- to extracellular potassium, the suggested delay in reabsorption of this cation by the veratrine-treated muscle[12] may later improve the response to the normal transmitter substance.

The majority of research into the physiology and pharmacology of myasthenia has pointed toward a chemical defect between the nerve ending and the end plate, but recent technical advances in recording transmembrane potentials and their variation with cation movements open avenues for new thought as to etiology. What is called block or facilitation at the neuromuscular junction may really be a reflection of ionic imbalances across the muscle membrane. Events such as posttetanic facilitation, previously thought to be prejunctional,[25] may be the result of potassium leakage, and the classic response of the myasthenic patient to medications may be partially due to restoration of membrane conductance; the peculiar insensitivity to the methonium compounds[34] might result from an abnormally high transmembrane potential secondary to excessive potassium concentration within the muscle cell[35] as well as to a competitive type of neuromuscular, or junctional, block.

That the activity of the ion transport mechanism may be defective in myasthenia is suggested by the marked sensitivity to such agents as procaine, procaine amide, and quinine derivatives, which do not interfere with junctional events but seem to block cation movement at the membrane level.

The exact mode of action of the veratrum allkaloids on muscle is still not clear. It is tempting to compare the properties of these steroid compounds with others, such as the cardiac glycosides, but the analogy seems clearly to fail when considering potassium exchange in acute experiments. Digitalis hastens repolarization[18] while veratrine greatly prolongs it. In addition, while lanatoside C has anticholinesterase properties, veratridine apparently does not. Though digitalis blocks the reentry of potassium into the red cell, veratrine has shown no such activity in preliminary experiments.[36]

Though such differences have been noted, the general similarity in chemical structure and action of cardiac glycosides and veratridine or cevadine suggests a common mode of action. Neither group of compounds exerts its muscle effects in acute experiments until the membrane has been depolarized, and neither owes its inotropic properties to any alteration in prejunctional events.

Attempts to clarify some of these problems are in progress, and it is hoped that an oral preparation of veratridine, cevadine, or veratrine can be utilized in more prolonged treatment of myasthenic patients. A more clear-cut pharmacologic rationale for the use of the veratrum alkaloids or chemical derivatives thereof may be available after the transmembrane muscle potential is measured in human beings.

SUMMARY AND CONCLUSIONS

These experiments afford some evidence that at least part of the classic veratrine effect is demonstrable in human skeletal muscle. Vera-

trine seems capable of inducing human muscle to perform more work per given stimulus. The alkaloid, given alone intraarterially, does not alter neuromuscular transmission but produces both tetanic responses and contracture after the membrane has been depolarized. Since the tetanic phase was not always observed in these studies and since veratridine, cevadine, or veratrine always produced an increase of contractile force, it is assumed that the contracture phase is the chief factor in the inotropic action of these agents. The apparent clinical similarity between the veratrine response and myotonia on both percussion and nerve stimulation is not supported by the electrical records since the prolonged shortening of muscle after veratrine is not associated with the electrical tetanus seen in myotonia.

The studies of potassium transport carried out here are fragmentary and inconsistent but may indicate that veratrine induces a slight net loss of potassium.

The administration of acetylcholine and veratridine in various doses and sequences has shown that the latter is unable to enhance or reverse the prompt or late depression of action potentials induced by the former, or products of its hydrolysis. The veratrum alkaloids in the doses used did not show any significant decurarizing activity. A mixture of d-tubocurarine and veratridine given together acted as curare alone. The augmented mechanical response after veratrine was always greater than the maximum posttetanic potentiation which could be elicited in normal subjects.

Neostigmine produced a characteristic decay in action potentials in healthy control subjects and a transient repair in patients with myasthenia gravis. In both, however, the force of contraction could be increased with this agent, indicating that it probably has some direct effect on the membrane in addition to its usual anticholinesterase activity. Veratrine evoked a much greater mechanical response than neostigmine in both healthy and myasthenic subjects without changing the action potentials in either.

These studies suggest that the integrated muscle action potential is not a reliable indicator of either junctional processes or the mechanical events following partial or complete membrane depolarization. Changes in transmembrane electrical potential due to blockage of cation efflux or influx may alter the number or amplitude of discharging units quite as effectively as competitive or depolarizing block at the neuromuscular junction, and, clearly, the strength of muscle contraction in both groups of patients studied need bear no direct relation to the surface action potential.

The clinical trials with veratrine in myasthenia gravis are encouraging and will be extended. Since the veratrum alkaloids do not impede the response of the myasthenic patient to standard anticholinesterase compounds, future treatment of this disease may involve using both.

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Superficial and deep reflexes in spinal cord injuries

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THE PRESENCE OF superficial abdominal reflexes in complete transverse lesions of the spinal cord in man has been documented but a few times in the literature.[1–4]

In 1954, in routine neurologic examinations of 2 verified cases of completely transected transverse lesions of the spinal cord with levels at the sixth thoracic segment, the superficial abdominal and cremasteric reflexes were found to be present. This aroused our curiosity and led to the following study utilizing patients with anatomically transected spinal cords and physiologically complete and physiologically incomplete lesions. The superficial abdominal and cremasteric as well as the deep reflexes, that is, the muscle-stretch reflexes of the abdominal wall – iliac, costal, pubic and rectus abdominis – were studied.

MATERIAL

In the anatomically complete lesions, there were 11 patients with severed spinal cords verified at surgery, ranging in age from 20 to 34 years. Injuries in 10 of these patients were of four to twelve years' duration, the remaining patient having been injured only seven months before. The levels of anatomic severance varied from the first to the seventh dorsal spinal cord segments. The cause of severance in 9 patients was a gunshot wound; in 2, fracture dislocation of the spinal vertebra.

A second group of 22 patients, aged 19 to 60 years, with physiologically complete lesions, had injuries ranging in duration from two to eleven years. The cause of injury in 21 was vertebral fracture dislocations; 1 lesion was due to a gunshot wound. Level of injury varied from the fifth to the eighth cervical segments in 16 patients and from the first to the fifth dorsal segments, respectively, in 6.

There were 15 patients, 24 to 60 years of age, with physiologically incomplete spinal cord lesions. The duration since injury ranged from eight months to eleven years and levels of injury were from the fifth to the eighth cervical segments. The cause of injury in 14 was fracture dislocation and in 1 a vascular anomaly of the cervical cord.

SUPERFICIAL REFLEXES

The superficial *abdominal reflexes* in this study were grouped as the upper and lower abdominals on the right and left sides (Table 1). When present, there was a homolateral contraction of the abdominal muscles resulting in a deviation of the linea alba and of the umbilicus.

Two types of stimulus were used – the scratch of a dull pin in each quadrant of the abdominal wall and the use of cold, via ether. We were on the alert for spread or spasm, that is, spread of stimulation causing contraction of neighboring muscles, such as the whole abdominal wall or some contraction of the muscles of the lower extremities. This spread or spasm might or might not be associated with a local response, but these data will be the purpose of another study.

When scratch was used as a stimulus in 11 patients with anatomically complete lesions, a local reflex was found in 24, or 54.4%, of 44 quadrants. In contrast, when ether was used, 15 of the 44 quadrants contracted, giving an incidence of 34%.

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TABLE 1
SUPERFICIAL REFLEXES ELICITED BY SCRATCH AND COLD STIMULI IN PATIENTS WITH SPINAL CORD INJURIES

Type of lesion	*Anatomically complete*	*Physiologically complete*	*Physiologically incomplete*
Number of patients tested	11	22	15
Local abdominal reflex (Per cent of quadrants)			
Scratch stimulus	54.4%	51.1%	45.0%
Cold stimulus	34.0%	12.5%	16.6%
Local cremasteric reflex (Per cent of sides)			
Scratch stimulus	22.7%	34.0%	20.0%
Cold stimulus	68.1%	11.3%	6.6%

In the 22 patients with physiologically complete lesions, 45, or 51.1%, of the 88 quadrants contracted after a scratch stimulus. When cold was used on these patients, 11, or 12.5%, of a total of 88 quadrants contracted.

Local contraction was elicited in 27, or 45%, of 60 quadrants in 15 patients with physiologically incomplete lesions on scratch stimulus; when cold was used, only 10, or 16.6%, of 60 quadrants contracted locally.

The *cremasteric reflex* was present on 5, or 22.7%, of 22 sides tested in patients with anatomically complete lesions, using scratch stimulus (Table 1). When cold was used as a stimulus, the local response occurred in 15, or 68.1%, of the 22 sides tested. Thus, as far as cremasteric reflexes in the anatomically complete lesions were concerned, cold was a more effective stimulus than scratch in eliciting local response.

In the physiologically complete lesions, scratch elicited the cremasteric reflexes in 15, or 34.0%, of 44 sides tested. Only 5 local responses, or 11.3%, were observed out of 44 sides tested when cold stimulus was applied.

Scratch elicited 6 cremasteric reflexes, or 20%, in 30 sides tested and cold 2 responses, or 6.6%, out of 30 sides in the physiologically incomplete lesions.

Thus, it can readily be seen that in patients with physiologically complete and incomplete lesions, scratch was a better stimulus in eliciting the cremasteric reflexes than cold.

DEEP MUSCLE, MUSCLE-STRETCH, OR PERIOSTEAL REFLEXES

The iliac, costal, pubic, and rectus abdominis (recti) reflexes of the abdominal wall were studied. The iliac reflex, a contraction of the lower abdominal wall, was elicited by tapping over each iliac crest. The costal reflex was effected by a sharp tap with the reflex hammer on or below each costal margin on either side in the nipple line and consisted of contraction of abdominal muscles toward the costal margin. Tapping over the symphysis pubis elicited the pubic reflex, consisting, when present, of a contraction of abdominal muscles, particularly the recti abdominis, and, sometimes, a contraction of the adductors of the thighs. The recti reflexes were any local contraction resulting from tapping each upper and lower rectus abdominis briskly.

In studying the above reflexes, we were on the alert for spread or spasm of neighboring muscles.

The results of this study are given in Table 2. In patients with anatomically complete lesions, the *iliac reflex* was found in 8, or 36.3%, of 22 areas tested. In the physiologically complete cases, iliac reflexes were found in 10, or 22.7%, of 44 areas tested. There were 30 areas tested in the physiologically incomplete cases, and the reflexes were obtained in 19, or 63.3%.

Costal reflexes were found in 15, or 68.1%, out of the 22 areas tested, in patients with

TABLE 2
COMPARISON OF LOCAL RESPONSE IN SUPERFICIAL AND DEEP REFLEXES IN PATIENTS WITH SPINAL CORD INJURIES

Type of lesion	*Anatomically complete*	*Physiologically complete*	*Physiologically incomplete*
Number of patients	11	22	15
Superficial reflexes (scratch stimuli)			
Abdominal (per cent of quadrants)	54.5%	51.1%	45.0%
Cremasteric (per cent of sides)	22.7%	34.0%	20.0%
Deep reflexes (percussion stimuli)			
Iliac (per cent of sides)	36.3%	22.7%	63.3%
Costal (per cent of sides)	68.1%	54.5%	76.6%
Pubic	54.5%	36.3%	66.6%
Recti (per cent of quadrants)	38.6%	13.6%	38.3%

anatomically complete lesions; in the physiologically complete lesions group, this reflex was found 24 (54.5%) of 44 times. This reflex was present in 23, or 76.6%, of 30 areas tested in patients with physiologically incomplete lesions.

Upon tapping over the symphysis pubis to elicit a *pubic reflex* in the 11 patients with anatomically complete lesions, a local contraction of the recti abdominis downward was noted 6 times (54.5%). With physiologically complete lesions, 8, or 36.3%, of 22 patients showed this reflex. In patients with physiologically incomplete lesions, 10, or 66.6%, of 15 patients responded in this manner.

In order to effect a *recti reflex* in patients with anatomically complete lesions, each upper and lower rectus of the abdominal wall was tapped sharply with a reflex hammer. A local reflex response was found in 17, or 38.6%, of the 44 quadrants tested. With physiologically complete lesions, response was elicited in 12, or 13.6%, of 88 quadrants tested. Patients with physiologically incomplete lesions responded locally in 23, or 38.3%, of 60 quadrants that were tested.

RESULTS

A comparison was made between the superficial and the deep reflexes in the spinal cord injuries (Table 2). With the scratch method in the series of 11 patients with anatomically complete lesions, the abdominal reflex was present in 54.5% of quadrants and cremasteric reflex in 22.7% of sides. Percussion stimulus gave the following results: iliac, 36.3%; costal, 68.1%; pubic, 54.5%; and recti, 38.6% of areas tested. The majority of responses were obtained from scratch in the superficial abdominal and tapping in costal and pubic areas.

In the group of 22 patients with physiologically complete lesions, the superficial reflexes obtained by scratch such as the abdominals were present in 51.1%; the cremasteric reflexes in 34%. On percussion, the deep reflexes such as the iliac were found in 22.7%, costal in 54.5%, pubic in 36.3%, and recti in 13.6% of the stimulated areas. Here, the superficial abdominal, by scratch, and the costal reflexes, by tapping, were in the majority.

In 15 patients with physiologically incomplete lesions, the superficial reflexes elicited by scratch were the abdominal in 45%; the cremasteric, 20%. The deep reflexes elicited by percussion were the iliac, 63.3%; costal, 76.6%; pubic, 66.6%; and recti, 38.3%. The percussion stimulus in the costal, pubic, and iliac areas elicited the majority of responses.

Thus, if comparisons are made from areas and stimuli, it is apparent that the scratch stimulus is the most effective for the superficial abdominal reflex. Of the deep muscle reflexes, the costal reflex is present in over 50% of the anatomically and physiologically complete lesions. In the physiologically incomplete lesions with some sensory recovery, however, there

TABLE 3

RELATIONSHIP OF RECOVERY OF MOTION AND SENSATION, OR BOTH, TO THE PRESENCE OF ABDOMINAL REFLEXES IN 15 PATIENTS WITH PHYSIOLOGICALLY INCOMPLETE LESIONS

	Per cent of quadrants	*Per cent of patients*
Abdominal reflex	45.0	
Touch recovery	41.6	
Pain recovery	25.0	
Cold recovery	30.0	
Motor recovery		53.3

were higher responses from the iliac, costal, and pubic areas. In the usual classic upper motor neuron lesion, it would be expected that the superficial abdominal reflex by means of scratch stimulus would be low and the deep muscle reflexes – the iliac, costal, pubic, and recti – much higher. This trend was noted only slightly in the physiologically incomplete lesions.

The relationship of recovery of motion sensation, or both, to the presence of abdominal reflexes in 15 patients with physiologically incomplete lesions in spinal cord injuries is shown in Table 3.

In 15 patients with physiologically incomplete lesions of the spinal cord, the abdominal reflex was found in 27, or 45%, of the 60 quadrants. Imperfect motor recovery recurred in 8 patients, or 53.3%, of cases. Imperfect touch recovery was found in 25, or 41.6%; imperfect pain in 15, or 25%; and imperfect cold in 18, or 30%, of 60 quadrants. We do not feel that 45% presence of abdominal reflexes is significant enough when compared to 54.5% of anatomically complete and 51.1% of physiologically complete lesions. Therefore, the presence or absence of imperfect sensory recovery or motor recovery in spinal cord lesions could not be correlated with the presence of abdominal reflexes nor was it of prognostic significance.

DISCUSSION

The abdominal skin reflex was first described by Rosenbach[5] in 1876. Comprehensive reviews on this reflex were done by Van Rinjberk[6] in 1937, by Wartenburg[7] in 1944, and others. Various authors have given diverse figures as to the presence or absence of the superficial abdominal reflex in normal man. In studies of a large series, Müller and Seidelmann[8] found that the superficial abdominal reflex was absent in only 1 of 1,000 men. In a very recent review on the cutaneous-abdominal reflexes, Medonick[9] found these reflexes to be absent in 16.5% of 2,500 nonneurologic admissions to a general hospital and absent in only 8.4% of 1,000 psychoneurotic patients.

Kuhn,[10] in a study of 25 men with verified anatomic transections of the spinal cord, D2 to D12, found superficial abdominal reflexes in 7 of 25 patients. In 3 of the 7, the response was limited to one abdominal quadrant.

Ford[11] stated that the abdominal reflexes may be elicited in the newborn in about one-third of all the cases and that the response obtained was rather diffuse reaction that involved extremities and was probably different from the adult response. He further stated that the true abdominal responses appear between the sixth month and the end of the first year. Harlem and Lonnum,[12] upon examination of 200 full-term healthy infants during the first week of life, found the abdominal reflex in all to be of a definite pattern. Since the pyramidal tracts had not matured, one must consider the infant's abdominal reflex to be a simple one.

Wartenburg[7] stated that "the greatest diagnostic significance of the abdominal-skin reflex lies in the fact that it is abolished in the presence of a lesion of the pyramidal tract and that this constitutes a valuable pyramidal sign. In the evaluation of the behavior of the abdominal-skin reflex, in the presence of a pyramidal tract lesion, even when there is a definite involvement of the pyramidal tracts, the abdominal-skin reflex may still be present or may

return soon. This is true, especially with such pathologic conditions as amyotrophic lateral sclerosis, spastic paralysis, infantile hemiplegia, and congenital spastic diplegia of Little. The abdominal-skin reflex may return before the lesion is healed. Its strength is not proportional to the severity of the pyramidal tract lesion, and in cases of multiple sclerosis it may be lost early when all other signs of pyramidal tract involvement are lacking."

Bronisch[2] believed that a sluggish, absent, or readily exhaustible abdominal reflex may indicate either direct damage in the reflex arc of the corresponding segments or a proximal lesion in the pyramidal tracts. Besides a simple spinal reflex arc, the central cerebral influence is of decisive importance for the occurrence of the abdominal reflex. In addition, he stated that there are several exceptions which have as yet not been explained – the abdominal reflexes can be obtained even after a transverse section of the cord or they may return after having been absent. He does not, however, distinguish between abdominal skin and the abdominal muscle reflexes.

Monrad-Krohn[13] stated that the abdominal reflex is a cerebral reflex that is diminished or absent in pyramidal and in peripheral motor abdominal lesions. He[14] also suggests that the occurrence of abdominal reflex, such as reported by Dejerine and Long in a case of complete transverse lesion of the cord, might have been a pathologic type of abnormal reflex. Some of the distinguishing features in this reflex are a longer latent period, with spread or spasm, and the need of a stronger stimulus for elicitation.

Pollock and associates,[1] in a study of anatomically complete spinal cord injuries of man, stated that the abdominal reflexes were generally absent until the ninth thoracic segment was reached in descending order, when the upper abdominal reflexes were present and the lower ones were absent. However, with lesions at upper levels, an abdominal reflex could be elicited from one of the quadrants in 2 cases. In 1 case with a spinal cord defect of 6 cm. at the sixth thoracic level, all of the reflexes were elicited. The cremasteric reflexes were absent when the lesion was below the sixth thoracic level and were present in 3 of 12 cases when the lesion was above this level.

Teasdall and Magladerry[15] made a study of the superficial abdominal reflexes, including latency by muscle action potentials. In normal adults, they found that short latencies were compatible only with basic spinal mechanisms. Random spread to contralateral sides occurred normally in patients with hemiplegia with and without hemianesthesia; latencies varied considerably. They conclude that abdominal reflexes depend basically on spinal mechanisms. Spread in these subjects is dependent upon intact central motor pathways. This we question. Increased latency and decreased briskness result from central motor damage unless concomitant sensory loss is present. This occurrence suggests the existence of an active central inhibitory effect on abnormal reflexes, mediated by intact sensory pathways.

CONCLUSIONS

1. The superficial abdominal reflexes in anatomically complete, physiologically complete, and physiologically incomplete spinal cord lesions were present in 54.5, 51.1, and 45% of tested quadrants, respectively.

2. In our experience, scratch as a stimulus in eliciting the superficial abdominal reflexes was much better than cold.

3. Cold elicited the cremasteric reflexes in 68% of the anatomically complete lesions, compared to a 22.7% incidence after scratch stimulus. In the physiologically complete lesion and the physiologically incomplete lesion groups, however, scratch gave a better response than cold.

4. Although the deep muscle reflexes of the abdominal wall were found in a fair percentage of cases, there was not the classic reverse decrease in percentage found in the superficial abdominal reflexes.

5. We could not correlate presence or absence of sensation with the presence of the abdominal reflex in anatomically complete, physiologically complete, or physiologically incomplete spinal cord lesions, and neither was it of prognostic significance. However, one could assume that the high incidence of abdominal reflexes in anatomically complete lesions would indicate the return to a simple reflex devoid of centripetal control.

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Influence of mesencephalic and diencephalic stimulation on limbic system seizures

A behavioral and electroencephalographic study in the cat

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INTRODUCTION

AFTER THE CLASSIC WORK of Dempsey and Morison,[1–4] many other investigators demonstrated altered cerebral electrical activity and excitability following brain stem stimulation and ablation.[5–15] Facilitatory and inhibitatory functions have been ascribed to the reticular and diffuse projection systems located in this region of the brain, especially for cortical evoked potentials and induced motor movements. The question is whether or not the brain stem reticular or recruiting systems tend to inhibit or facilitate the production, propagation, duration, and variability of seizure activity.

The following experiments were designed to evaluate the effect of electrically stimulating the activating and recruiting systems of the mesencephalon and diencephalon upon seizures elicited from the limbic system.

TECHNIC

The experiments were performed in 44 cats. After 0.5% procaine anesthesia was infiltrated into the animal's scalp, triple stainless-steel electrodes were inserted into the subcortical structures and screws were inserted in the skull to the cortical surface. The subcortical needles had tips 1 mm. long, 0.5 mm. in diameter, and 1.5 mm. apart; 24 needles were placed in various subcortical structures and 4 on the cortex. Cortical electrodes were invariably placed in the anterior sigmoid gyrus and the gyrus suprasylvius medius. Bipolar electrical stimulations and recordings were made with a Grass square wave stimulator and electroencephalograph. Stimulation parameters were 1.5 to 5 volts, 10 to 30 cycles a second, one millisecond pulse, and five seconds' duration. Behavioral changes during the electrical stimulations and after-discharges were correlated with the electroencephalographic recordings.

In 65 experimental observations, the number of stimulations per observation varied from 40 to 96. The experimental design consisted of stimulations spaced at constant intervals of two to four minutes. The series was divided into 2 to 4 blocks, each containing 10 to 30 stimulations. Within alternate blocks, the electrically elicited seizures were preceded by a stimulus* applied to the brain stem. The preceding stimulus to the brain stem occurred within one-half to one minute before the seizure-producing stimulus was applied to the limbic structure. The seizure durations, electrical patterns, and behavioral changes associated

*The stimulus applied to the brain stem is occasionally referred to as an activating stimulus, although behavioral activation did not accompany all stimulations. In the illustrations, the location of the activating stimulus is designated by the most familiar structure at the point of stimulation. This serves as an identification or signpost at the anatomical site stimulated and is not exclusive of the unnamed structures which also are implicated by the stimulus.

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with activation were recorded. In 14 experiments, 10 cc. of 0.5% glucose in water was administered every hour and the catheterized urine output maintained at 3 to 5 cc. an hour. No major differences in seizure duration and electrical patterns were noted between hydrated and nonhydrated animals.

After the completion of each experiment, the brains were perfused with saline solution which was followed by a 10% solution of formaldehyde containing potassium ferricyanide. The brains were then serially sectioned, and the points of stimulation and recording were identified histologically. Anatomic sites of recording and stimulation were correlated with electroencephalographic and behavioral changes. Points of stimulation in the brain stem were plotted on frontal sections according to the atlas of Jasper and Ajmone-Marsan[15] (Fig. 1). Analyses of the seizure duration distributions revealed lack of normality, homoscedasticity, and independence; thus, the t and F tests were not employed to determine significance of differences. However, the mean durations and variances for each block of seizures were calculated in all experiments, and further analyses made by inspection.

RESULTS

Nonpreactivated seizures. Repeated stimulation of limbic system structures resulted in the production of seizures which did not appear to vary in their seizure characteristics. Once established, the pattern, propagation, and duration of an electrical after-discharge presented a more or less constant configuration. Occasional deviations from this observation occurred (Figs. 2 and 3). As illustrated, cingulate gyrus seizures occasionally spread to the hippocampus and induced a hippocampal-system discharge. However, the discharge was not thought to be due to repeatedly evoked, electrically induced seizures, since it occurred only 9 times out of 124 consecutively induced discharges. Although this type of cingulate discharge is not directly due to the cingulate-applied stimulus, it was considered as such in the analysis.

As previously mentioned,[17] repeated stimulation of the cingulate gyrus is conducive to sleep spindle formation (Figs. 3, 4, and 5). The animal is somnolent at this time. Sleep spindles are preserved during the slow 5 to 6 per second cingulate discharge pattern (first half of the seizures, 11:38 and 11:46) but not during the fast electrical pattern (second half of the discharge) which is thought to represent an induced hippocampal discharge resulting from the propagated cingulate seizure (Fig. 3). An unusual exception to these observations is demonstrated in the control or nonpreactivated hippocampal discharges during which time the sleep spindle persisted in the motor and sensory cortices (Fig. 6, Experiment 33). Sleep spindles are not necessarily indicative of increased seizure activity or vice versa.

In contrast to other structures, repeated elicitation of hippocampal seizures is usually accompanied by a definite tendency for the seizure duration to become progressively longer. Since such a mechanism may effectively counteract any opposite effect which might otherwise result from the preactivating stimulus, interpretation of the results becomes difficult. A comparison of the blocks of preactivated seizures with their respective preceding control blocks (Fig. 6) illustrates this difficulty. If one took this mechanism into consideration and were allowed to assume that the fourth block of preactivated seizures should have lasted, for example, four hundred or more seconds, if not preactivated – the two hundred and ninety-nine seconds in preactivated block 4 would represent decreased, rather than increased, duration. Such speculation was not feasible or justified; thus, direct and objective comparisons were made between the various blocks and the results tabulated (Fig. 7).

Another peculiar characteristic which occasionally appeared with repeated hippocampal discharges consisted of progressively increased variability of the seizure duration. Such a change was best illustrated in Figure 8, Block 3. The total seizure duration for this block was greater than each of the previous ones. However, its variability was much greater, and the difference in duration may be considered less significant. In the analysis, the seizure durations were evaluated and compared irrespective of the changes in variability which may have existed. Variability also was compared independently and the results plotted accordingly (Fig. 7).

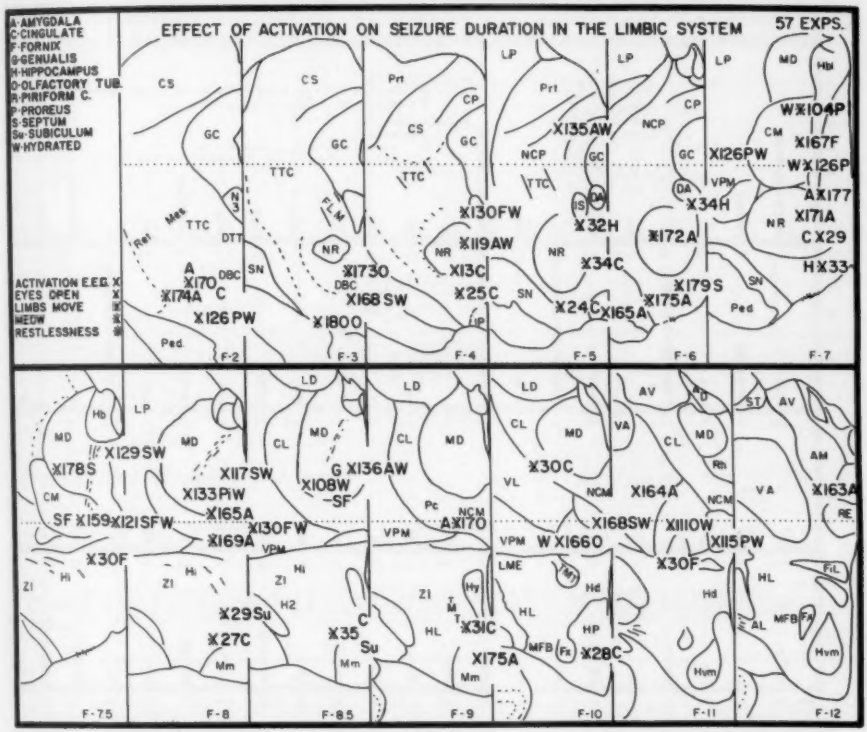

FIG. 1. The approximate points of stimulation in the brain stem activating and recruiting systems are plotted in 13 frontal planes. The experiment number identifies the localization, the accompanying letter the structure from which the seizures were elicited. Note insert for further details as to type of behavioral activation. Horizontal dotted lines represent horizontal zero, the vertical solid lines sagittal zero plane. AL, ansa lenticularis; CL, nucleus centralis lateralis; CM, nucleus centrum medianum; CP, commissure posterior; CS, colliculus superior; DA, Nucleus of Darkschewitsch; DBC, Decussatio brachiorum conjunctivorum; EW, nucleus of Edinger-Westphal; FiL, nucleus filiformis; FX, fornix; GC, Griseum centrale; H_1, H_2, Forel's fields; HBL, nucleus habenularis lateralis; HL, hypothalamus lateralis; HP, hypothalamus posterior; HVM, hypothalamus ventromedialis; IP, nucleus interpeduncularis; IS, nucleus interstitialis; LD, nucleus lateralis dorsalis; LME, lamina medullaris externa; LP, nucleus lateralis posterior; MD, Nucleus medialis dorsalis; MFB, Median forebrain bundle; MM, corpus mammillare; NCP, nucleus commissule posterior; NVM, nucleus hypothalamic ventromedialis; NR, nucleus ruber; PC, nucleus paracentralis; Ped, pedunculus cerebralis; Prt, praetectum; RE, nucleus reuniens; Ret. Mes., substantia reticularis mesencephalica; SN, substantia nigra; St, stria terminalis; THP, Tractus habenulopeduncularis; TMT, tractus mammillothalamicus; TTC, Tractus tegmentalis centralis; VA, nucleus ventralis anterior; VL, nucleus ventralis lateralis; VPM, nucleus ventralis posteromedialis; ZI, zona incerta.

It appeared as if the degree of interdependence between seizures varied from very little to a more or less maximal degree. The maximal interdependence is illustrated in Figure 6. As will be noted, each of the long-duration seizures was followed by the shortest seizure in its respective block of 21 seizures. Subsequent seizures gradually returned to previous durations. In Figure 8, Block 3, an obvious alternation is found between long and short seizures except for 2 instances. Such changes are suggestive of long-lasting seizures as hav-

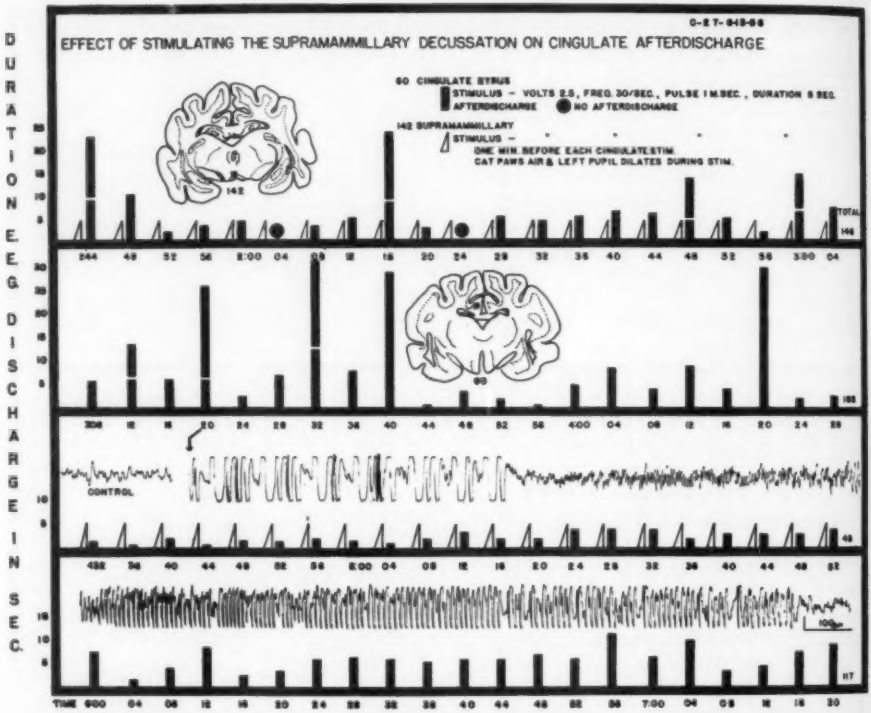
EFFECT OF STIMULATING THE SUPRAMAMMILLARY DECUSSATION ON CINGULATE AFTERDISCHARGE
60 CINGULATE GYRUS
STIMULUS – VOLTS 2.5, FREQ. 30/SEC., PULSE 1 M.SEC., DURATION 5 SEC.
AFTERDISCHARGE NO AFTERDISCHARGE
142 SUPRAMAMMILLARY
STIMULUS –
ONE MIN. BEFORE EACH CINGULATE STIM.
CAT PAWS AIR & LEFT PUPIL DILATES DURING STIM.
DURATION EEG DISCHARGE IN SEC.
CONTROL
TIME

FIG. 2. Experiment 27: 84 consecutive stimulations of the cingulate gyrus at four minute intervals. Alternate blocks of 21 stimulations are preceded by stimulation of the posterior hypothalamus. Bars interrupted with white lines represent the cessation of the typical cingulate electrical activity and beginning of hippocampal activity as revealed in the inserted recording. Note text for discussion and interpretation of seizure duration changes.

ing a definite influence on the duration of subsequent seizures – another factor which makes interpretation difficult in this type of design.

It is of further interest that throughout a sequence of plotted seizure durations, a pattern of waves or undulations appeared (Fig. 5, Blocks 1, 2, 3). This pattern is thought to reflect an oscillating mechanism which is fundamental to physiologic processes.

Repeated amygdaloid discharges occasionally induced hippocampal or septal system seizures. This type of propagation, however, just as mentioned for the cingulate gyrus discharges, was very infrequent. No major motor seizures developed after repeated stimulations.

Preactivated seizures. Stimulation of the brain stem structures apparently did not alter the pattern of the discharge or degree of propagation. Localized brain stem electrical afterdischarges propagated from the limbic system did not show any change in amplitude, configuration, or pattern during the blocks in which the brain stem was stimulated. Changes, if any, were primarily concerned with the duration and variability of the seizure as illustrated in Figure 7. Even in the instances of altered duration induced by the preceding activating stimulus, there were no alterations of pattern or degree of spread. Brain stem stimulation did not increase or decrease the tendency for cingulate gyrus and amygdaloid sei-

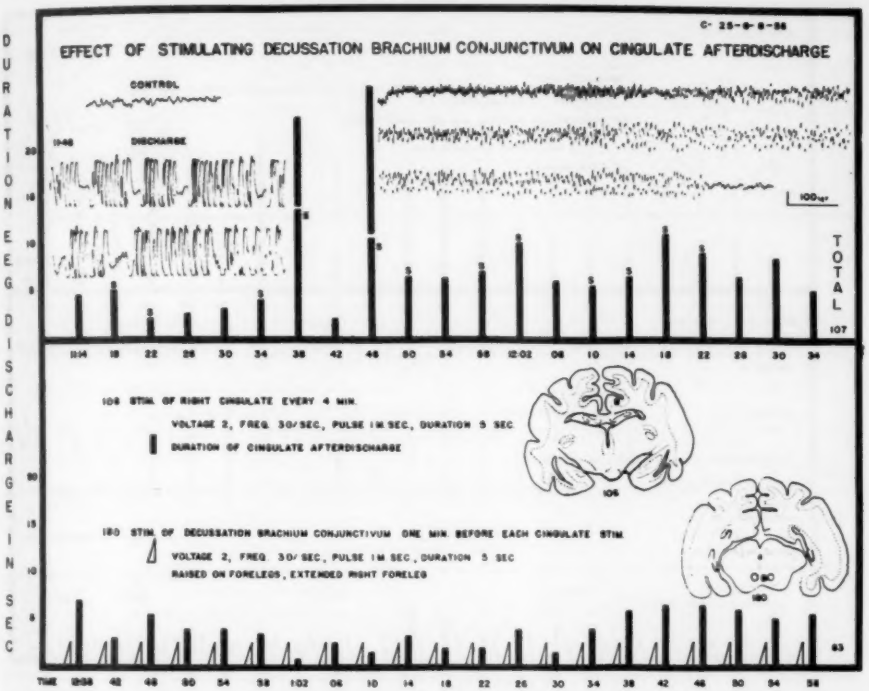
EFFECT OF STIMULATING DECUSSATION BRACHIUM CONJUNCTIVUM ON CINGULATE AFTERDISCHARGE
CONTROL
DISCHARGE
TOTAL
DURATION EEG DISCHARGE IN SEC
108 STIM. OF RIGHT CINGULATE EVERY 4 MIN.
VOLTAGE 2, FREQ. 30/SEC., PULSE 1 M SEC., DURATION 5 SEC.
DURATION OF CINGULATE AFTERDISCHARGE
180 STIM. OF DECUSSATION BRACHIUM CONJUNCTIVUM ONE MIN. BEFORE EACH CINGULATE STIM.
VOLTAGE 2, FREQ. 30/SEC., PULSE 1 M SEC., DURATION 5 SEC.
RAISED ON FORELEGS, EXTENDED RIGHT FORELEG
TIME

FIG. 3. Experiment 25: 42 consecutive cingulate gyrus seizures every four minutes. The second block of seizures contains stimulation of the mesencephalon (Insert 180) one minute before the induced seizures. Triangles represent mesencephalic stimulation and the vertical bars seizure duration. Note the cingulate discharge which has propagated to the hippocampus and induced a secondary discharge in that structure which is then reflected back to the cingulate gyrus (11:46 Insert). First half represents typical cingulate activity during the time sleep spindles appeared (S) and persisted in the motor and sensory cortex. The second half consists of propagated activity from the hippocampal system during the time the sleep spindles disappeared.

zures to spread to the hippocampal and septal systems. Stimulation in the diencephalon at points which produced recruiting responses did not materially alter the after-discharge characteristics. Results appeared to be independent of the laterality of the activating stimulus in comparison to that of the limbic structure seizure from which the seizure was elicited.

In Figure 5, sleep spindles occur rather frequently during each of the 2 blocks (1 and 3) of nonpreactivated cingulate gyrus seizures. However, during activated blocks 2 and 4, sleep spindles are not present during the first three-fourths of each series; however, sleep spindles are present in the last fourth. This is indicative of a physiologic adaptation to the activating stimulus. Possibly, other physiologic processes may similarly become less affected by the repetitive activating stimulus as time goes on; thus, its effect on seizures may not always be consistent throughout a given series of stimulations. Occasionally, there also appeared to be decreased behavioral response to the activating stimulus during the latter portion of each series.

The extreme variability which may normally occur with hippocampal- and fornix-induced seizures may not be influenced by an activating stimulus (Fig. 9), although seizure duration may reveal definite changes.

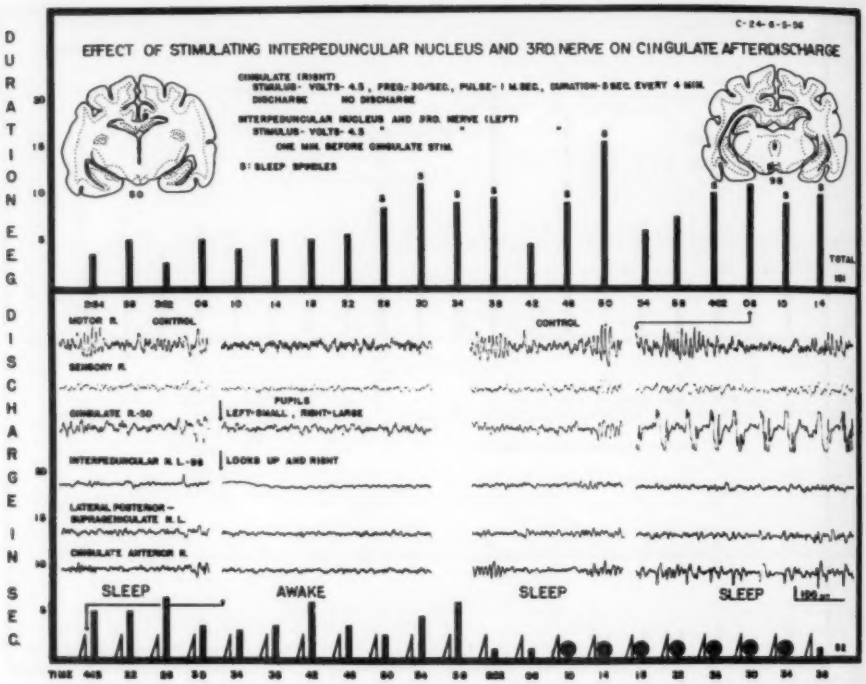

FIG. 4. Experiment 24: 42 consecutive stimulations of the cingulate gyrus spaced four minutes apart. A significant increase in the average duration is manifest during the second block which contains preactivating stimuli applied to the ventral mesencephalon. Note the preservation of sleep spindles in the motor cortex during the cingulate discharge (4:06) (S over bar is omitted), in contrast to their disappearance immediately after the activating stimulus (4:18).

Seizure interdependence which may characteristically exist, as mentioned previously, is not always altered by the activating stimuli (Fig. 6, Block 4). The oscillations in the seizure duration patterns to which we previously referred may or may not be altered by the preactivating stimuli (Fig. 5, Block 2, 4).

Mesencephalic stimulation effects. Behaviorally, the responses in the cats varied from no movement to opening the eyes, dilating the pupils, hissing, meowing, turning the head, elevating a limb, and continued restlessness. Electroencephalographic patterns in all instances consisted of a low-voltage fast activity described by Moruzzi and Magoun.[5] Sleep spindles were invariably extinguished (Fig. 4). Stimulation of the midventral mesencephalic tegmental region with 30 cycles a second appeared to have a greater tendency to reduce, rather than increase, seizure duration and variability (Fig. 7). The presence or absence of behavioral activation did not appear to influence the character of the results (Figs. 1 and 7). In 19 experiments, 45 comparisons were made. The mean seizure duration was reduced in 26 comparisons in 18 experiments and increased in 19 comparisons in 15 experiments. Variability was reduced in 27 comparisons in 17 experiments and increased in 18 comparisons in 13 experiments. The combined variability and mean duration were reduced in 20 comparisons in 17 experiments and increased in only 13 comparisons in 19 experiments.

Apparent, long-lasting depressant effects from mesencephalic and hypothalamic stimulation were displayed in some animals (Figs.

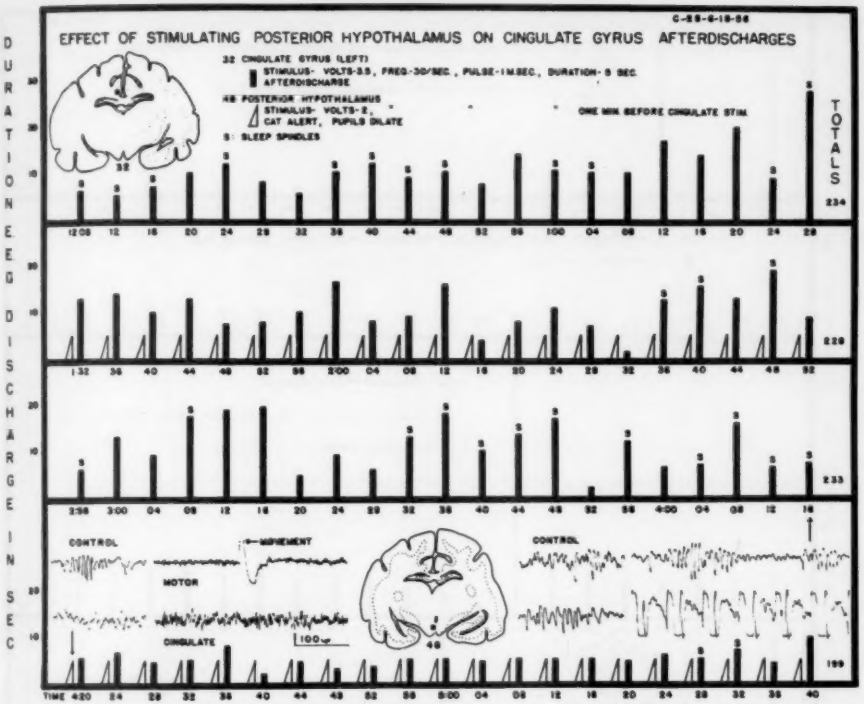

FIG. 5. Experiment 28: 84 consecutive stimulations of the cingulate gyrus divided into 4 blocks, which are alternately preactivated by hypothalamic (Insert 48) stimulation. Note the presence of sleep spindles (S) throughout the nonpreactivated block. However, sleep spindles only appear in the last fourth of each of the preactivated blocks. Note the over-all undulating pattern of the discharge duration — except for the last block.

2 and 11). In order to further evaluate this observation, the experimental design was changed in Experiment 34 (Fig. 10). The predominate alteration in design consisted of inserting 1 block of 21 activating brain stem stimuli which were not followed by seizures; in the fourth subsequent block, brain stem stimuli were followed by a preactivated block. The first block of 21 cingulate stimulations, four minutes apart, produced seizures in all but 1. The second block of 21 stimulations was located in the ventromedial mesencephalon. During this block, no stimuli were applied to the cingulate gyrus. Block number 3 consisted of isolated cingulate gyrus stimulations similar to the first. Here, the first 3 cingulate stimulations were not effective in producing a discharge. In the fourth block, the mesencephalic and cingulate stimulations were combined and a dramatic reduction in seizure activity ensued. This demonstrates a combination of immediate and prolonged effects of mesencephalic stimulation upon seizures from the cingulate gyrus.

Posterior hypothalamic stimulation effects. Stimulation of the posterior hypothalamus produced an electrical activation pattern in all instances. Behavioral changes varied just as did those mentioned under mesencephalic stimulation. Mean seizure duration was decreased in 13 comparisons in 8 experiments and increased in 5 comparisons in 3 experiments. Variability was decreased in 11 comparisons in 7 experiments and increased in 7

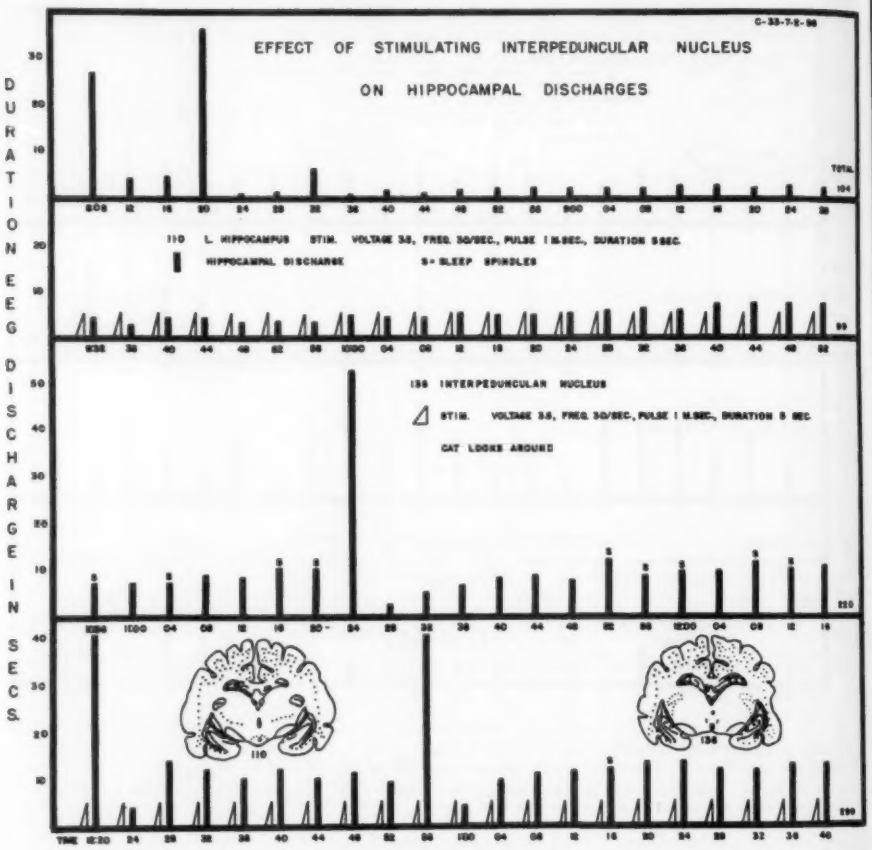
EFFECT OF STIMULATING INTERPEDUNCULAR NUCLEUS
ON HIPPOCAMPAL DISCHARGES
DURATION EEG DISCHARGE IN SECS.
110 L. HIPPOCAMPUS STIM. VOLTAGE 3.0, FREQ. 30/SEC., PULSE 1 M.SEC., DURATION 5 SEC.
HIPPOCAMPAL DISCHARGE
S= SLEEP SPINDLES
136 INTERPEDUNCULAR NUCLEUS
STIM. VOLTAGE 3.0, FREQ. 30/SEC., PULSE 1 M.SEC., DURATION 5 SEC.
CAT LOOKS AROUND
110
136

FIG. 6. Experiment 33: 84 consecutive stimulations of the hippocampus at four-minute intervals. Activation stimulus one minute before each hippocampal discharge. This illustrates a progressively increasing hippocampal discharge duration, in spite of the injected midmesencephalic activation. The presence of sleep spindles (S) during hippocampal discharges is unusual and is discussed in the text.

comparisons in 5 experiments. Just as with mesencephalic stimulation, combined effects occurring most frequently were decreases in seizure duration and variability.

In these methods of analysis, several points tend to be obscured or overlooked. Thus, a detailed analysis of the effect of hypothalamic stimulation on seizures is being presented in 2 experiments (Fig. 11, Experiment 29; Fig. 2, Experiment 27). In Figure 11, the activating stimuli were located in the hypothalamus, second block of seizures; and the cingulate gyrus, fourth block of seizures. Every four minutes, 84 seizures were elicited from the subiculum. If one compared the second hypothalamic activation block with the first nonpreactivated control block, mean seizure duration was apparently reduced – due to hypothalamic stimulation. The third block, which represented the control, should have had a return of seizure duration commensurate with that in the first block. This theoretically ex-

SEIZURE VARIABILITY

MEAN SEIZURE DURATION

	Increase				Decrease			
Increase	A	H	O	S	A	C	H	O
	119	33	180	130	135	170	32	173
	119	34	180	130	170			
	*165		180	168				
	174			179	P			
					126			
Decrease	A	H	O	P	A	C	H	O
	135	32	173	126	136	13	34	180
	165				170	24	33	180
					172	25	33	
					172	34	32	
					175			
					*165			
					174			
					174			
					P	S		
					126	168		

MESENCEPHALIC

	Increase			Decrease			
Increase	F	Su		C			
	30	35		35			
				28			
				28			
Decrease	A	C	Su	C	F	S	Su
	175	31	29	27	30	179	35
		31	29	27			
				27			
				31			
				28			

HYPOTHALAMIC

ACTIVATING STRUCTURE

	Increase				Decrease		
Increase	A	F	G	O	A	C	SF
	*164	30	108	111	*163	30	108
	*165	*167	108		*164	30	108
	*165		108		171		121
	171				171		121
	174				171		
	174						
	*163						
	170						
	P	Pi	S				
	115	133	117				
	126		129				
	126		129				
			130				
			130				
			159				
			159				
			159				
Decrease	A	G	P	S	A	F	O	P
	170	108	115	178	*163	30	*166	115
	170		126		*163	30	*166	115
			126		*163			126
			104		136			126
					*164			104
					136			
					174			
					174			
						Pi		S
						133		117
						169		117
						169		117
								168
								168
								178

THALAMIC

FIG. 7. Effect of mesencephalic, hypothalamic, and thalamic stimulation upon mean seizure duration and variability: The entries are made with reference to whether or not the preactivated seizure blocks displayed an increased or decreased variability and duration when compared to the immediately preceding and following control or nonpreactivated seizure blocks. The experiment number from which the comparison was obtained was inserted in the appropriate square under the letter that designates the structure from which the seizures were elicited. (A, amygdala; C, cingulate; F, fornix; G, genulais (gyrus); H, hippocampus; O, olfactory tubercle; P, proreus (gyrus); S, septum; SF, septum-fornix; SU, subiculum).

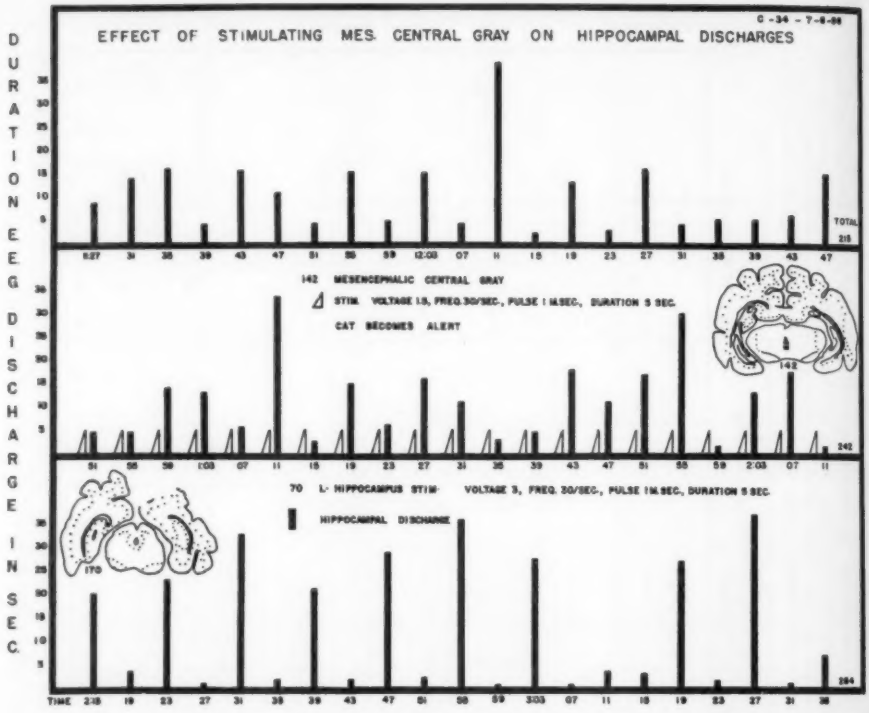
C-34 - 7-8-38
EFFECT OF STIMULATING MES. CENTRAL GRAY ON HIPPOCAMPAL DISCHARGES
DURATION EEG DISCHARGE IN SEC.
TOTAL 215
142 MESENCEPHALIC CENTRAL GRAY
STIM. VOLTAGE 1.5, FREQ. 30/SEC., PULSE 1 M.SEC., DURATION 5 SEC.
CAT BECOMES ALERT
142
242
70 L- HIPPOCAMPUS STIM. VOLTAGE 3, FREQ. 30/SEC., PULSE 1M.SEC., DURATION 5 SEC.
HIPPOCAMPAL DISCHARGE
170
284
TIME

FIG. 8. Experiment 34: 63 consecutive stimulations of the hippocampus every four minutes illustrates a characteristically increased seizure duration as the experiment progresses. In addition, this graph illustrates a marked concomitant increase in variability which is thought to reduce the significance of the increased duration.

pected result did not occur. Thus, one was inclined to apply 2 possible explanations:

1] The preparation was deteriorating.

2] The effect produced during the second block was prolonged through most of the third block. The fourth block showed increased seizure duration during the subsequent cingulate activation, which indicates a preparation which was definitely not deteriorating. Therefore, the results obtained in the third block represented a prolonged effect from the changes which took place during the second block. A humoral effect was suggested, since it was sustained over such a long period of time.

Figure 2, Experiment 27, illustrates a series of 84 consecutive cingulate gyrus seizures which were divided into 4 blocks of 21 each. In the experimental design, the activating stimulus in the posterior hypothalamus was applied during the first and third blocks of the series. Note that the second control block showed an increased duration which, however, did not appear significantly greater than the first block. The lack of greater change may have been due to the prolonged effect of the hypothalamic stimulation employed in the first block. Superimposing a restimulation of the hypothalamus upon the apparent, long-lasting effects caused greater depression of seizure duration and variability, third block. This was followed by a fourth control block which showed an increase, as expected. However, it did not return to the same duration as attained in the second control block. This was

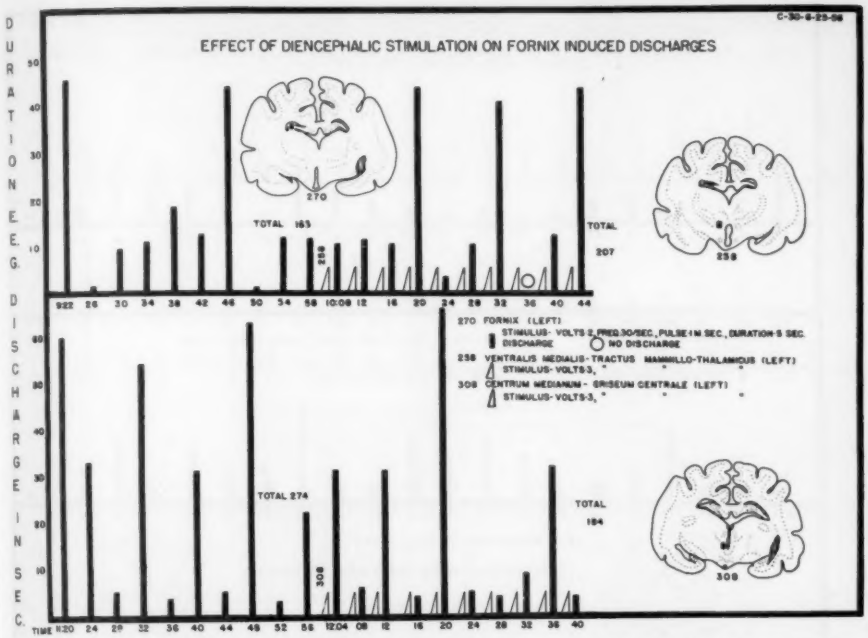
EFFECT OF DIENCEPHALIC STIMULATION ON FORNIX INDUCED DISCHARGES
DURATION E.E.G. DISCHARGE IN SEC.
TOTAL 163
TOTAL 207
TOTAL 274
TOTAL 184
270 FORNIX (LEFT)
STIMULUS- VOLTS 2, FREQ 30/SEC., PULSE 1 M SEC., DURATION 5 SEC.
DISCHARGE
NO DISCHARGE
258 VENTRALIS MEDIALIS - TRACTUS MAMMILLO-THALAMICUS (LEFT)
STIMULUS- VOLTS 3, " " "
308 CENTRUM MEDIANUM - GRISEUM CENTRALE (LEFT)
STIMULUS- VOLTS 3, " " "
TIME

FIG. 9. Experiment 30: 40 consecutive stimulations at four minute intervals in the fornix: This illustrates the characteristically increased variability in fornix seizures, which is not altered by diencephalic activation. However, the duration may have been affected.

thought due to a compounding of long-lasting effects from hypothalamic stimulation. Figure 5 represents a compounding of effects which do not become evident until the last block of seizures. In addition to the effect of the activating stimulus, one is again well aware that deterioration may be a contributing factor in this type of result. However, such a degree of abrupt change does not seem to appear unless the activating stimulus is added.

Thalamic stimulation effects. Stimulation of the thalamus produced electroencephalographic activation patterns in all instances. Behavioral changes in the animals, although infrequent, usually consisted of opening the eyes or generalized nonspecific body movements (Fig. 1). Frequencies of 10 per second, which produced recruiting responses, did not influence seizures differently from frequencies of 30 per second. The presence or absence of significant recruiting responses did not appear to be related to the observed effects on seizure duration. In 17 experiments and 26 comparisons, seizures revealed a combined increased duration and variability (Fig. 7). In 14 experiments and 26 comparisons, seizures revealed a combined, decreased seizure duration and variability. Mean seizure duration was increased in 37 comparisons in 18 experiments and decreased in 34 comparisons in 16 experiments.

DISCUSSION

These results demonstrate a strong inclination toward homeostasis of central excitability.[18] Under such conditions, only major or central tendencies become evident: The midventral mesencephalic and hypothalamic regions tend to decrease seizure duration and variability. The midline thalamic intralaminar structures, on the other hand, may enhance seizure duration and variability. It must be reemphasized that major tendencies are being expressed, since these structures also displayed

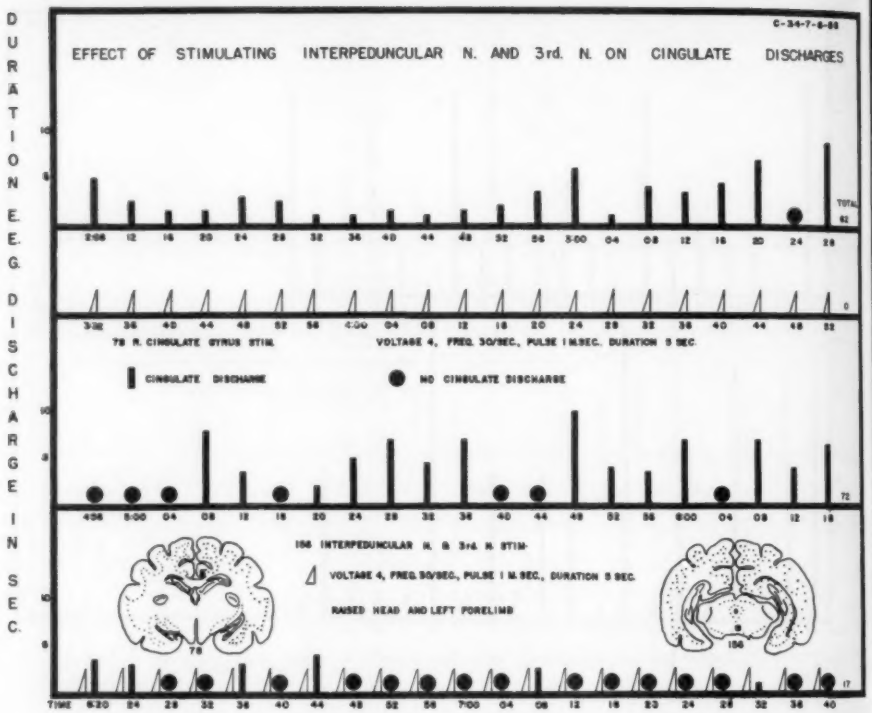
EFFECT OF STIMULATING INTERPEDUNCULAR N. AND 3rd. N. ON CINGULATE DISCHARGES
DURATION E.E.G. DISCHARGE IN SEC.
79 R. CINGULATE GYRUS STIM.
VOLTAGE 4, FREQ. 50/SEC., PULSE 1 M.SEC. DURATION 5 SEC.
CINGULATE DISCHARGE
NO CINGULATE DISCHARGE
156 INTERPEDUNCULAR N. & 3rd. N. STIM.
VOLTAGE 4, FREQ. 50/SEC., PULSE 1 M. SEC., DURATION 5 SEC.
RAISED HEAD AND LEFT FORELIMB
TIME

FIG. 10. Experiment 34: In contrast to previously described experimental designs, a block of 21 activating stimuli were applied between two blocks of cingulate gyrus seizures. Note the dropping out of seizures at the beginning of the cingulate block which immediately follows the activation block. The final block is a combination of the two; activating stimulus (Insert 156) precedes the seizure-inducing stimulus by one minute.

an almost equal ability to exert opposite effects to those assigned. The differences were small, especially for the thalamus.

Observed effects could not be related to the presence or absence of behavioral and electrical activation. Apparently, brain stem stimulation induced changes in mechanisms which may or may not have coexisted with, and been independent of, the activation phenomena.

Both immediate and prolonged brain stem influences were observed. The immediate effects were thought to be mediated through neuronal pathways which provide a bidirectional conduction of impulses. An example of such an anatomic system has recently been brought to our attention by Nauta.[13] Fibers running dorsally in the stria medularis and ventrally through the hypothalamus form a complete circuit between the forebrain limbic structures and the brain stem. Undoubtedly, other fiber systems enter into such circuitry but are as yet unknown. Since cerebellar stimulation is known to alter cortical seizure activity,[20] stimulation of cerebellar efferents in the brain stem may also account for the limbic system seizure changes. However, it is difficult to determine whether the cerebellar system exerts influences through pathways already mentioned or through others which are still unknown.

Long-lasting effects as were best noted with hypothalamic stimulation suggest the participation of humoral influences. Although it is hazardous to relate specific humoral effects to

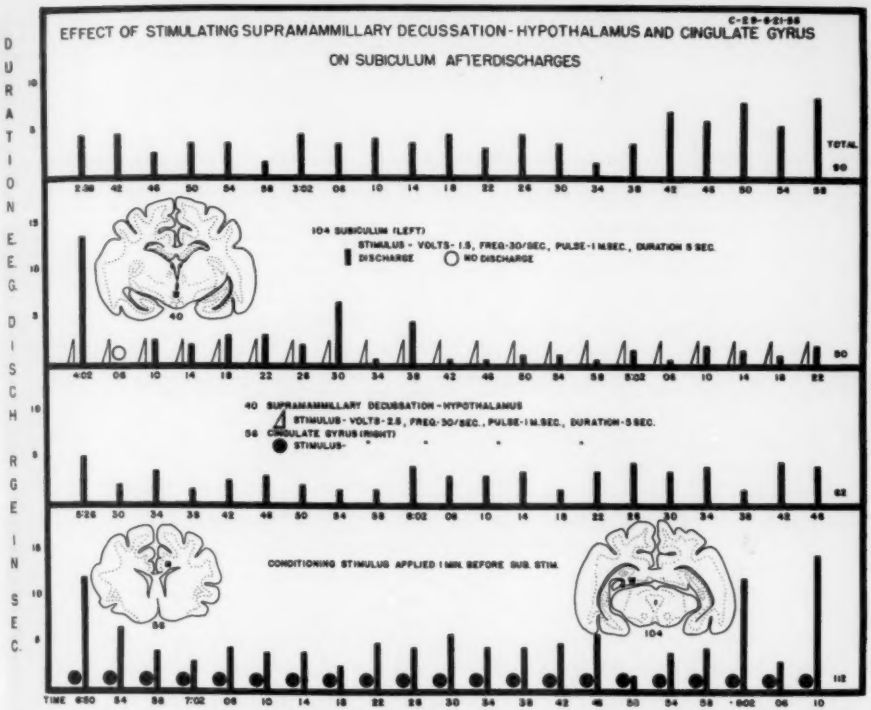
EFFECT OF STIMULATING SUPRAMAMMILLARY DECUSSATION - HYPOTHALAMUS AND CINGULATE GYRUS
ON SUBICULUM AFTERDISCHARGES
DURATION EEG DISCHARGE IN SEC.
TOTAL
104 SUBICULUM (LEFT)
STIMULUS - VOLTS - 1.5, FREQ-30/SEC., PULSE-1 M.SEC., DURATION 5 SEC.
DISCHARGE
NO DISCHARGE
40 SUPRAMAMMILLARY DECUSSATION - HYPOTHALAMUS
STIMULUS - VOLTS - 2.5, FREQ-30/SEC., PULSE-1 M.SEC., DURATION-5 SEC.
56 CINGULATE GYRUS (RIGHT)
STIMULUS-
CONDITIONING STIMULUS APPLIED 1 MIN. BEFORE SUB. STIM.
TIME

FIG. 11. Experiment 29: 84 consecutive stimulations of the subiculum (Insert 104) every four minutes. Note the reduction in seizure duration induced by the hypothalamic (Insert 40) preactivating stimulus and the increased duration induced by the cingulate gyrus (Insert 56) preactivation stimuli.

this problem, one cannot refrain from referring to compounds such as the catechol amines and related substances. These substances have been demonstrated to produce synaptic inhibition or depression.[21] Furthermore, they have been isolated from the hypothalamus, diencephalon, and mesencephalon.[22] Stimulation of the same structures has been known to cause secretion of adrenalin and noradrenalin from the adrenals.[23] Our activating stimuli, therefore, undoubtedly implicated mechanisms dealing with the elaboration of these and probably other related compounds as yet unknown. It is difficult to avoid a discussion of brain stem influence on seizure duration without noting that humoral mechanisms may play an important role in this problem and may account more directly for some of our findings. Derangement of the humoral controlling mechanisms possibly contributes to status epilepticus in addition to other seizure states. Because of these observations and implications, an evaluation of the presence or absence of humoral changes and their significance, in various seizure states, should be investigated further.

SUMMARY

The effects of brain stem stimulation on electrically induced limbic system seizures were studied in 44 cats.

Brain stem stimulation was correlated with behavioral and electroencephalographic changes, and its influence on seizure production, propagation, duration, and variability was evaluated.

Seizures which were repeatedly and regu-

larly produced had a tendency to maintain fixed characteristics.[17,24,25] Furthermore, brain stem stimulation did not appear to alter the character of the discharge – except for its duration and variability.

Mesencephalic and hypothalamic stimulation seemed to reduce seizure duration and variability; the thalamus was inclined in the opposite direction. It must be emphasized that these structures displayed an almost equal ability to exert opposite effects from those assigned to them.

The effects of brain stem stimulation on seizures were interpreted as being both short and long lasting: short effects caused by direct neuronal stimulation, and long effects caused by induced humoral changes.

Seizure duration and variability appeared to be independent of the behavioral and electroencephalographic changes commonly described as activation.

Duration and variability changes from thalamic stimulation appeared to be independent of the thalamic recruiting responses.

Sleep spindles appeared more frequently during discharges from the cingulate gyrus than from other limbic structures and were not associated with increased seizure duration or propagation.

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Studies on abnormal movement: cerebellar ataxia

Fred A. Mettler, M.D., and Fernando Orioli, M.D.

TOGETHER with tremor and chorea, the term ataxia suffers from certain ambiguities which introduce imprecision, if not confusion, to diagnosis. The essential difficulties in the inexact use of the term stem from the vague impression[1] that almost any irregular or uncoordinated movement is a sort of ataxia[2] and that the presence of such uncoordinated activity bespeaks the existence of a disturbance of cerebellar function, regardless of where the lesion is situated. Thus, spinal ataxias may be erroneously viewed as being essentially due to an interference with impulses ultimately destined to reach the cerebellum. Recent anatomic investigations have made it clear that the medullary nuclei upon which the dorsal funiculi of the spinal cord project do not send collaterals to the cerebellum, and there is good clinical precedent not only for questioning the common identity of the cause of spinal and cerebellar ataxias but also for attempting to define the latter as clearly as possible in order to achieve diagnostic precision. In subjecting this matter to inquiry, we shall attempt [1] to inquire into what is meant by ataxia, [2] to see if there are different types, and, [3] if there are, to establish a definite correlation between them and particular kinds of clinical diagnoses. Finally, an effort will be made to delimit those conditions under which ataxia appears in cerebellar disturbances.

In its classical sense, ataxia—a lack of order in arrangement—is a useful, but inadequately restricted, term. The word came into use in the seventeenth century and was ultimately applied by Spencer[1] to the motor "irregularities in arrangement" resulting from cerebellar disease. Before that time, Flourens "found that when a small portion of the cerebellum of a pigeon was extirpated, the bird experienced a lack of steadiness in walking. This unsteadiness increased as larger amounts of the cerebellum were removed and, with complete ablation, there appeared to be a total lack of 'coordination'. In 1828 he observed that lesions in the semicircular canals produced a loss of equilibrium and in-co-ordination of movements. Correlating the results of this study with his work on the cerebellum, Flourens maintained that both organs were associated with the co-ordination of movement and maintenance of equilibrium, terms which were long applied to the cerebellum until it was shown by Sherrington that the entire neural system is co-ordinated, and it was realized that equilibrium can be impaired in many different ways."[2]

Restriction can be applied to the meaning of the word by qualifying it with adjectives such as spinal, cerebellar, or frontal. Our attention must be directed to inquiring into the ways wherein these varieties of ataxia differ. Before we do this, it is necessary to clarify how ataxia differs from disequilibrium. If such a distinction cannot be achieved, we shall find ourselves involved in the same confusions which attach to the word, incoordination.

Disequilibrium as contrasted with ataxia. Such a distinction is important since ataxia and disequilibrium can both be produced by a single cerebellar lesion and because the participation of a relatively small portion of the cerebellum, notably the "flocculo-nodular lobe" plus the uvula (and perhaps pyramis) and deep nuclei, in equilibratory function has created the erroneous impression that cerebellar disorders are essentially dysfunctions of equilibrium and that ataxia is inextricably bound up with disequilibrium. That only certain por-

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tions of the cerebellum are concerned with equilibratory activity was actually known during the last century[3] but it was Dow[4] who first pointed out that the marked equilibratory disturbance which follows removal of the nodulus and uvula "is not found after extirpation of other parts of the cerebellar vermis."

We know very little about the effect of flocculonodular dysfunction in man since the eighth nerve itself is usually involved in lesions which affect the human flocculonodular lobe. In carnivores, the results of damage to this apparatus are more severe than in lower primates like monkeys; we have reason to believe that what we see in the latter animals would also be true of man. Lesions of the vestibular portion of the cerebellum[5] result in primates which "were unable to walk during the first postoperative hours at which time they lay on their bellies with the limbs abducted and sprawled. They were able to stand, sit or walk within the first 48 hours after operation and to climb shortly afterwards. Animals from which the nodulus and uvula were ablated were never able to run. All animals showed a great reluctance to move about and grimly resisted dislodgement from stable positions, clinging very strongly to whatever they had at hand. They never struggled, jumped or ran as do normal animals under such circumstances. Forced forward falling was present in all animals and occurred whenever they were disturbed and/or had to move around more than they used to do spontaneously. Sometimes one had the impression that they threw themselves forcibly on their bellies to avoid being caught, since they were unable to run away.

"The pattern of disequilibrium was similar in floccular as well as in nodulo-uvular ablations but was less pronounced and more transient in the former. However, the manner of sitting, standing and walking was significantly different. . . .

"Nodulo-uvular monkeys walked with the 4 limbs abducted, the anterior stiffly extended and the posterior flexed, the buttocks being carried upon or very close to the floor. Following floccular removal, the animals walked with the legs extended and the arms slightly flexed (as a 'fighting bull'). The same pattern was present during running but under such circumstances the monkey deviated alternately to one and then to the other side, finally falling forcibly to the floor or hitting against the wall (they looked like a person riding a bicycle for the first time)."[5]

Disturbances of this type occurred primarily in movements of the whole body and in the maintenance of posture rather than as motor activity disability of individual body segments. Characteristic of disequilibrium are turning of the head and eyes to one side; nystagmus; falling, rolling, and spiraling movements; and an oscillatory swaying disturbance in the maintenance of posture or during walking.

Cerebellar ataxia

In contrast to the generalized impairment of disequilibrium are the unsteadiness of the extremities; ataxic (intention), simple (resting), and epipraxic and propaxic (postural) tremors and diminished motor performance; decreased resistance to passive movements of the limbs; and postural asymmetry which characterize removal of nonvestibular cerebellar cortex. Such cortical lesions do not, however, produce the severe uncompensable defects and the unsteadiness noted above. In fact, the ataxia is never maximal unless the deep nuclei or brachium conjunctivum are damaged, and the disturbance is not evident until movement is attempted.

Since damage of the deep nuclei always produces a certain amount of interference with the fibers of the vestibular cerebellum, the ataxia produced in this way is often tainted with disequilibratory factors; therefore, it is preferable to study ataxia after section of the brachium conjunctivum.

Carrea and Mettler describe ataxia objectively as "a purposeless disturbance of associated or individual voluntary movements, usually involving large muscle masses such as those of the trunk, shoulder, and pelvic girdle. It is characterized by an inappropriate range, rate and strength of each of the various components of the motor act and by an improper sequence of those components. Electromyographically ataxia is manifested as a decomposition of movement consisting of abnormal duration and sequences of bursts of contraction and relaxation of the agonists and antagonists of a joint, usually a large joint."[5,6]

When patients with cerebellar disease contract their muscles, periodic, alternating epi-

sodes of positive and negative muscle activity are displayed. The positive phases are very forceful and sudden. Smooth contraction of agonist and antagonist is thus rendered impossible. Such an unsustained state of muscular activity results in difficulty in arranging the limb in space; this may be so marked that the patient shows astasia, a serious impairment of standing, and, of course, abasia, or inability to walk. Symptoms such as hypermetria, decomposition of movement, dysdiadochokinesis, and intention tremor are merely manifestations of ataxia in accordance with the clinical test employed and the movement examined.

Asynergia

A word is in order here with regard to the distinction between asynergia and ataxia. Babinski coined the word, synergy, and added the symptom of asynergy[7] to the cerebellar triad of Luciani (astasia, asthenia, and atonia). Babinski also introduced diadochokinesis and its similar disturbance, adiadochokinesis. According to Babinski,[8] the common signs of cerebellar disturbance were dysmetria, asynergia, and adiadochokinesia, to which he added cerebellar catalepsy—a sign that has never been widely accepted. In connection with this latter sign, Babinski pointed out that many patients with cerebellar disorder are able to hold positions—even very abnormal ones, such as lying on their backs with the legs in the air—with no evidence of unsteadiness.

The fundamental physiologic alterations behind all cerebellar signs were considered by Babinski to be asynergy and inertia. Asynergy was visualized as a disturbance in the mechanism and order of muscular contraction. This condition might be termed incoordination, but Babinski[9] called it a disorder of motor association between large muscle groups. Because of asynergia, the participating muscles act without the moderating influence of their antagonists. It is posisble, Babinski said, to apply this explanation to intention tremor also. The associative function is inherent in the cerebellar system, and it is not altered in tabes dorsalis. Thus, Babinski's own manner of using the term made it the practical equivalent of ataxia. The usage of other writers, however, was so broad as to include practically all coordinative difficulties. With the realization that disequilibrium had to be distinguished from the effects of nonvestibular cerebellar disorder, the terms, asynergia and dysnergia seem to have much too broad a connotation to be of value in describing cerebellar disorders, for they comprehend not only ataxic and disequilibratory phenomena but also other defects in coordination of motor performance.

Spinal ataxia

Ataxia due to disease of the spinal cord—spinal ataxia—differs so markedly from cerebellar ataxia that one wonders whether this term should not be changed. It is, in fact, a derivative of Romberg's[10] locomotor ataxia; however, there is often more widespread pathology in locomotor ataxia than is found in the spinal cord alone, and it is very doubtful whether the classical symptomatology could be reproduced by severance of the dorsal columns and without actual radicular disease.

Locomotor ataxia usually begins with a rather unspecific unsteadiness of gait, accompanied by sensations of heaviness in the legs, fatigue, and a positive Romberg sign, but a peculiarly irregular, loose, and disorderly type of locomotion, in marked contrast to the alternating character of true cerebellar ataxia, ultimately develops.

The common factor in spinal or dorsal root and cerebellar ataxia is the patient's inability to regulate the degree of contraction of the muscles, but, in the former condition, the proprioceptive circuit is broken and the affected limb flails off in a wild, loose fashion. In contrast to this, the proprioceptive reflex mechanism is intact in cerebellar ataxia, and an antagonistic reflex contraction is rapidly activated which also proceeds beyond normal check limits, overstretches the original contracting muscle, and activates a proprioceptive contraction of opposite sign. Out of such alternate contraction and overstretching of opposing muscles, the alternating nature of cerebellar disorder appears to arise; no such forceful self-propagating alternation is possible in spinal ataxia. Duchenne[11] long ago insisted on clinically differentiating locomotor ataxia from cerebellar ataxia. He applied the phrase *titubation asynergique* to the motor disturbances of locomotor ataxia and considered them a true incoordination of movement. He likened cerebellar ataxia to the vertiginous state seen in drunkenness and termed it *titubation ver-*

tigineux. It can scarcely be overemphasized that locomotor ataxia is always much looser in quality than typical cerebellar ataxia, which has a characteristic, forceful, positive quality and a peculiar springy appearance. In tabetic, as opposed to cerebellar, ataxia, the movements are without orientation from the very beginning. Without visual guidance, they are aggravated. They are not influenced by the speed of movement to the same extent that cerebellar movements are, and they do not have a repetitive tendency. Cerebellar ataxia follows a more or less constant phasic pattern.

Frontal ataxia

It may be seriously doubted whether the so-called frontal ataxia that is found in the clinical literature actually exists except as an artifact from pressure exerted elsewhere.[12] Such a condition has never been produced in experimental physiology, and Rouquier[13] could see no cerebellar symptoms, either direct or crossed, in over 150 patients with frontal trauma. Under the name of frontal homolateral syndrome, he did, however, describe vestibular and extrapyramidal symptoms.

Combined disabilities

In concluding our comments about the nature of ataxia, we may say that there would appear to be but 2 forms—cerebellar and spinal—which should be easily distinguishable from each other. If cerebellar ataxia existed, as, for example, in the heredodegenerative ataxia of Marie, and the pathology necessary for the appearance of spinal ataxia developed, as sometimes occurs in Marie's familial ataxia, spinal would supplant cerebellar ataxia since the forceful alternating character of the latter could not endure in the absence of proprioceptive reflexes.

Cerebellar ataxia must be clearly distinguished from disequilibration in company with which it frequently does occur. Here again the alternating character and forceful, springy nature distinguishing cerebellar ataxia are of primary importance. When added to cerebellar dysfunction, disequilibration is likely to be submerged in hypokinesia.[14]

THE PHYSIOLOGIC CAUSE OF CEREBELLAR ATAXIA

According to Holmes,[15] the main disturbance in cerebellar ataxia is a deficiency in postural tonus. Andre Thomas[16] attributed a fundamental role to an insufficiency of the antagonist muscles.

In Walshe's[17] opinion, the critical element in cerebellar function is to be sought in a close functional relationship between the cerebral motor cortex and cerebellum and not in any direct participation of the cerebellum in those reflex activities of brain stem and cord which subserve the elements of coordination. He criticized the hypothesis that the relation of agonist and antagonist—simple synergia—is a function of the cerebellum. It is incredible, Walshe said, that this high level suprasegmental organ should be involved in the elementary processes of simple coordination which we know the simple spinal arc is able to accomplish. If it were so, the reflex movements of decerebellate, thalamic, and pontospinal animals would be as ataxic as the voluntary movements of the decerebellate but otherwise intact animal. Walshe concluded that the cerebellum is an organ through which the cerebral motor cortex achieves the synthesis of the coordinated units which make up voluntary movement, and he correlated the postural components with the phasic components of coordinated voluntary movement.

Pollock and Davis[18] similarly found that removal of the cerebellum does not affect the coordinative muscular contractions occurring in certain tonic and phasic reflexes in decerebrate animals. Our own negative experience in searching for an alteration in the monosynaptic arc upon stimulation of the rubrospinal tract[19] and descending limb of the brachium conjunctivum[20] would also appear to be in accordance with Walshe's opinion.

With the exception of Altenburger's[21] study, few electromyographic studies cast much light on the pathophysiology of ataxia. Altenburger showed that voluntary movements are influenced by the cerebellum in such a way that the actions of different muscles are balanced one against another to reach the ultimate skilled movement. The cerebellum supports the function of the antagonist in continuous, slow, as well as in fast, movements. Studying the relation between agonists and antagonists in single movements in cerebellar disease, he found that slow voluntary movements can be performed by the agonists themselves. The dif-

ferent fasciculi in the muscle contract almost synchronously. In some cases, the antagonist also works, usually in periods which alternate with the agonist, but the contractions are weaker. In rapid movements, the checking of the movement by the antagonist is either not so precise as in the normal or is delayed or absent. Altenburger's analysis established a frame of reference into which subsequent theorizing has had to be fitted, and it has become apparent that critical new electrophysiologic studies would probably have to be conducted on the central nervous system itself. There have been many such studies on the afferent connections of the cerebellum but very few on its efferent connections.

STRUCTURAL SUBSTRATE OF ATAXIA

We will now examine the consequences of interrupting all of the principal afferent systems of the cerebellum and observe whether ataxia will result from such interference.

Dorsal columns

Destruction of the dorsal columns has not frequently been resorted to in this context since abundant clinical literature is already available on this subject. The effect, however, is not endurable spinal ataxia. For this to persist, the dorsal roots themselves must be damaged.

Spinocerebellar tracts

Experimental section of the spinocerebellar tracts has produced some widely divergent results due to the fact that spinal cord surgery is fraught with the production of artifacts resulting from postoperative edema, herniation of the cord, and the spread of scar tissue. The essentially negative results of Ferraro and Barrera[22] have made it clear that very little happens when the spinocerebellar tracts are cut and that what does happen has nothing in common with ataxia. In our own experience,[23] it has been possible to cut both spinocerebellar tracts and the restiform body in the same animal without producing any signs of cerebellar dysfunction.

When we have fulgurated the rubrospinal tract[19] in the medulla, the proximity of this to the spinocerebellar tracts usually resulted in very slight damage to one or the other. In most of the cases, only transitory cerebellar symptoms were observed. These were probably due to retraction of the cerebellum in order to visualize the side of the medulla.

Restiform body

Many writers have assumed that cerebellar symptoms follow lesions of the restiform body, but Ferraro and Barrera,[22] who made sections in the restiform body at different levels, do not concur. The symptoms they observed were qualitatively the same as those that followed lesions of the dorsal spinocerebellar tract. The only difference was one of intensity. The lesions of the restiform body were followed by more pronounced dysmetria, hypotonia, ipsilateral weakness, and diminution of reflexes; the symptoms were the same in type, regardless of the level of division, but their intensity was greater the higher the lesion was placed. There was no abnormal activity, such as rolling movements, spontaneous tremor at rest, intention tremor, or spontaneous nystagmus; transitory tremor was present in the acute stage, however.

On section of the restiform body in monkeys,[24] weakness, hypokinesia, and slight hypotonus of the ipsilateral limbs were the most noticeable symptoms, in addition to a moderate abduction of the upper limbs, more marked on the homolateral side, and a tendency to lean and fall to the side of the lesion in the acute stage. Sometimes, in later stages, such animals also fell to the opposite side. These results agree with those of Ferraro and Barrera.

It is probable that most of the severe cerebellar signs described by earlier writers and accepted by textbook writers as typical of restiform body damage were due to lesions which interfered with the posterior inferior cerebellar artery which supplies both the posterolateral medullary region and the cerebellum. Many of the early estimates of symptomatology were based on medullary softenings and were certainly of vascular origin. Such a case was described by Thomas.[25] This patient had a softening of the inferior cerebellar peduncle, motor difficulties, and disturbances in equilibrium. There was a sclerotic patch in the tegmentum and another softening in the cervical spinal cord. Thomas attributed the symptomatology to involvement of the vestibular root and of cerebellar fibers. Riley[26] is one of those who attribute the cerebellar signs encountered

in occlusion of the posterior inferior cerebellar artery to involvement of the direct spinocerebellar tract and restiform body. He was aware that anastomotic connections exist between the posterior inferior cerebellar artery and other arteries on the surface of the cerebellum whereas its medullary vessels are terminal. He therefore assumed that occlusion of the vessel would have little effect on the nutritive supply of the cerebellum. There is, however, no sharp distinction between the medulla and cerebellum on the basis of anastomotic and terminal supply; some terminal vessels do supply the deeper parts of the cerebellum, and cerebellar escape depends upon whether anastomotic channels will prove adequate when present. Adequacy depends upon a variety of factors.[27]

As a result of careful consideration of the clinical literature, it is apparent that what facts exist are in accordance with experimental findings. Thus, Merritt and Finland[28] encountered cerebellar symptoms in only 3 of their 6 cases of occlusion of the posterior inferior cerebellar artery; in the 1 case in which an autopsy was available and showed involvement of the restiform body, no cerebellar symptoms had existed. They encountered an expected, variable symptomatology reflecting differences in those portions of the neuraxis which are involved – a necessary consequence of differences not only in the condition of the involved vessel and the manner in which it is occluded but also in its anatomic distribution. A desirable frame of reference to bear in mind when making clinical diagnoses of this condition distinguishes between vestibular and nonvestibular cerebellar signs as well as medullary signs proper. There is no reason to suppose that involvement of the restiform body itself would precipitate any signs of the first 2 classes.

Brachium pontis

The experimental approach to the brachium pontis is difficult and, like the study of clinical material, has yielded conflicting results. No wholly satisfactory accounts of a lesion of significant size accurately limited to the brachium pontis have been reported. Torsion and rotation of the body with falling to the side of the lesion, rolling of the eyeballs, and deviation of the eyes have been described. Ferrier and Turner observed, moreover, incoordinated movements of the ipsilateral limbs, but these coincided with damage of the brachium conjunctivum. Turner and German[29] described similar symptoms in monkeys without tremor or ataxia of the classical cerebellar type. Transient dysmetria may be present. Clinically, Babinski[9] and Claude and Lejonne[30] attributed cerebellar symptoms to lesions of the middle cerebellar peduncle. On the other hand, if one analyzes the cases of Dejerine,[31] it is significant that, although some of them show lesions almost dividing the whole middle cerebellar peduncle, no cerebellar disturbances are mentioned.

We have not been successful thus far in completely severing the brachium pontis in the monkey without producing some other type of damage, but the symptomatology exhibited by cases in which this was attempted could all be attributed to fortuitous damage; none of these animals has exhibited ataxia.[23]

Olivocerebellar fibers

The difficulty which exists with regard to the pons is also encountered in connection with the olivocerebellar fibers. Lesions which involve these almost certainly involve other structures which tend to obscure the functional result.

Magendie described forceful movements after olivary lesions in animals and Meschede observed forceful rotatory movements in patients with large olivary lesions. Bechterew asserted that the inferior olives probably have some relationship with motor coordination and the maintenance of static postures and oculocephalogyric movements. According to Zand,[32] the inferior olives are the center for the coordination of antigravity muscles and play an important role in decerebrate rigidity. Luthy, however, could not confirm these findings. Myoclonia in the human being has been ascribed to lesions affecting the inferior olives or their connections, but, after an exhaustive study of the subject, Trelles[33] concluded that the only relationship which would withstand scrutiny was that of the so-called hypertrophic degeneration of the olives, with palatopharyngeal myoclonia—a correlation established by Davison, Riley, and Brock.[34] Although Schroeder Van der Kolk and various other older writers had attributed a coordinative role in speech movements to the inferior olives, Trelles states that the hypertrophic degeneration itself is

secondary to pathology in the opposite dentate nucleus or the tegmentum. Moyano[35] similarly maintained that demyelinization and sclerotic lesions of the inferior olives are very common in general paresis and, together with the cerebellar lesions, play an important part in the pathogenesis of the dysarthria of such patients.

Besta[36] sectioned the olivocerebellar connection in dogs by splitting the medulla. He described a progression of symptomatology through three stages:

Initially, his animals were extremely weak and prostrated, showing voluntary activity only when strongly stimulated. Proprioceptive and righting reflexes were abolished. A stage of improvement followed, during which time voluntary movement and proprioceptive and righting reflexes reappeared.

These manifestations culminated in a stable condition in which the postural reflexes were overactive and a dysmetric gait endured. This was similar to, but less pronounced than, that which follows cerebellar lesions.

Carrea, Reissig, and Mettler[37] placed lesions in the olives and found that "ablation of the caudal half of the olivary system produces results resembling ablations of the cerebellar vermis. The effect of ablation of the rostral half of the olivary complex resembles ablation of the cerebellar hemispheres and/or the flocculus."

An analysis of the symptoms observed in monkeys subjected to division of the olivocerebellar fibers by splitting the medulla[38] shows that marked general hypoactivity always ensued. This symptom, so often seen in lesions of the vestibular cerebellar system,[5] might be due to section of the vestibular fibers in the raphe of the medulla or to the incidental damage of the vestibular parts of the cerebellum. The attitude of the animals and, as a consequence, the gait (which was marked by extension and abduction of the forelimbs and flexion of the hindlimbs or flexion of the forelimbs and semiextension of the hindlimbs) are similar to signs described[5] after removal of either the cerebellar flocculus and the nodulus or the nodulus only in monkeys and lesions of different portions of the inferior olivary complex in the cat.[37] The findings of Brodal[39] on the anatomy of the olivocerebellar connections give a probable explanation of the curious similarity between cerebellar and direct olivary lesions; the rostral half of the medial accessory olive projects upon the flocculus, nodulus, and part of the uvula while the caudal part projects upon the uvula and remaining vermis in front of it. When the medulla was split, however, unavoidable damage of the nodulus and flocculus, both medial longitudinal fasciculi, and the vestibulospinal fibers in the raphe of the medulla makes it very difficult to attribute the attitudes described for these animals exclusively to interruption of the olivocerebellar fibers. Certainly no ataxia resulted from section of the olivocerebellar connection.

Vestibulocerebellar fibers

In differentiating between disequilibrium and ataxia we have already considered the consequences of impairment of the vestibulocerebellar apparatus. This subject has also been more fully discussed elsewhere.[5]

Cerebellum

In the foregoing, we have seen that ataxia does not result from experimentally induced lesions of the afferent cerebellar systems. The moment we damage the cerebellum, however, ataxia immediately becomes apparent. The nature and location of disability with lesions in different portions of the cerebellum have been fully considered by Carrea and Mettler.[5] The ataxia which follows lesion of the cortex of the corpus cerebelli is observed almost exclusively during voluntary activity and is always compensated for in a relatively short, though variable, period of time. On the other hand, ablation of the cerebellar nuclei is characterized by disturbance of associated, unlearned motor function—very often in association with impairment of voluntary, learned motor activity. Compensation, when it occurs, is always slow and incomplete. Lesions of the dentate and interposed nuclei produce intense ataxia with ataxic tremor occurring during voluntary and associated activity and during the maintenance of static postures as well as during kinetic activity. A similar picture follows cerebellar decortication when the nuclei are involved; the tremor is less conspicuous, however.

The dysfunction, including tremor, which follows lesions of the proximal part of the superior cerebellar peduncle is essentially similar to that which succeeds lesions of the dentate

and interposed nuclei. Ataxia is not, however, evoked by severance of the brachial fibers as they enter the thalamus nor even, in a considerable proportion of cases, by lesions in the red nucleus.[6] This seems to imply that ataxia can no longer be evoked once all the fibers of the decussation of the brachium conjunctivum have been passed. If the descending limb of the brachium conjunctivum (which arises as collaterals from the primary brachial fibers after decussation and makes its way into the spinal cord[20,40,41]) is taken into consideration, a possible explanation for the disappearance of ataxia, once the decussation has been passed, can be developed. Analysis of ataxia-producing lesions has shown that an impairment of conduction through both the rubrospinal tract and descending limb is a common factor.[42] However, uni- or bilateral destruction of the descending limb at the level of the upper pons by means of the Horsley-Clark technic does not produce definite ataxic disturbances nor does a lesion of the rubrospinal tract in the medulla alone or when combined with one of the descending fibers of the brachium conjunctivum.[19,20] Only marked hypokinesis and mild hypotonia are produced in the ipsilateral limbs when the rubrospinal tract is severed. Evidently all 3 efferent discharge routes of the brachium conjunctivum must be involved for ataxia to appear.

Rademaker asserted that bilateral labyrinthectomy in a decerebellated animal makes the cerebellar ataxia worse. In our hands, however, the addition of vestibular nerve section to section of the brachium conjunctivum and the vestibular nerves[14] does not intensify cerebellar ataxia itself. It does add a greater degree of disequilibrium to the picture. When the brachium and the vestibular nuclei were destroyed, similar results were obtained, but the animals were more deteriorated.

CONCLUSION

1. Only 2 forms of ataxia, spinal and cerebellar, can be distinguished, but it is necessary to differentiate between these two entities and, further, between them and disequilibrium. Disequilibrium and cerebellar ataxia often occur together.

Disequilibrium affects the bodily musculature as a whole and is usually accompanied by deviation of the head and nystagmus. Disturbance at rest is evidenced by the assumption of tense postures and a strong disinclination to move. The head is involved in the kinetic and static disturbances which result. Wide, deviated, and lunging forms of locomotion with rolling, swaying, and twisting all may be seen in disequilibrium.

Cerebellar ataxia is characterized by forceful, springy, alternating activity which, if of cortical origin, interferes with the active attempt to arrange the limbs and body more particularly than with the effort to hold truncal postures, although so-called postural and intention, or, as we prefer to call them, ataxic, tremors are true manifestations of ataxia as are a great variety of special abnormal tests such as dysdiadochokinesis, abasia, and so on. It can be produced only by damage of the cerebellum itself or of its principal efferent pathway, the brachium conjunctivum, before division of the latter after its mesencephalic decussation. Disequilibrium is evokable not only by injury to the vestibular system proper but also by interference with the flocculonodular lobe and its associated deep nuclei and connections. Spinal ataxia is due to destruction of afferent mechanisms at spinal levels. It is a loose, nonrepetitive, throwing type of disarrangement, which occurs primarily in the lower extremities.

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CASE REPORT

Horizontal conjugate gaze in brain stem lesions

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ANATOMICAL STUDY has revealed relationships that permit localization of a lesion in the pons to the findings of a peripheral facial paralysis and a paralytic type of horizontal conjugate gaze. Transient periods of forced horizontal conjugate gaze and of a defect in the horizontal conjugate gaze with a temporary peripheral facial palsy were observed in a patient receiving x-ray therapy for a medulloblastoma of the posterior fossa. The ocular findings of this patient are illustrated in this report.

CASE REPORT

This 31-year-old male was admitted with symptoms of a recurrent cerebellar medulloblastoma. One year previously, the lesion had been biopsied and this was followed by a course of x-ray therapy. He returned with symptoms of increasing ataxia in the arms and legs, increasing difficulty in walking, headache, and vomiting. During hospitalization, he became confused and lethargic and developed papilledema. Ventriculographic examination indicated a lesion of the posterior fossa, and suboccipital craniectomy disclosed a massive recurrence of the tumor in the left cerebellar hemisphere. Except for a residual neoplasm lateral to the midbrain and pons, the entire left cerebellar hemisphere was removed.

The patient improved rapidly postoperatively and was able to walk with assistance. Coarse nystagmus was present in all fields of gaze. The ataxia in arms and legs improved, and he developed pallor of the optic disks.

X-ray therapy was started twenty-six days after surgery. On the thirty-fourth postoperative day, the patient developed vertigo, left facial palsy, and inability to look to the left. Examination disclosed a minimal left peripheral facial palsy. At rest, the eyes were maintained in forced horizontal conjugate gaze to the right (Fig. 1). The patient could not voluntarily look to the left nor could he follow an object to the left. Voluntary and following movements were preserved in upward and downward conjugate gaze; however, the eyes were maintained in the same plane as the lateral position noted at rest. In the extremes of upward and downward conjugate gaze, the eyes could not be deviated from this plane to the left voluntarily or in following movements (Fig. 2). Rapid turning of the head to the left resulted in further lateral displacement of the right eye and further medial displacement of the left eye. When the turning of the head stopped, the eyes assumed their previous position of forced horizontal conjugate gaze noted at rest. On attempted closure of the eyelids, true Bell's phenomenon was not apparent; the eyes deviated upward but not laterally, that is, the forced conjugate gaze to the right was maintained. The pupils were equal and reacted to light. The patient was able to deviate the right eye medially when told to look at the end of his nose. This same phenomenon could be demonstrated in convergence testing with following movements. No nystagmus was present.

The eyes were in the primary position on the next day. When the eyes were deviated to the right on command, some delay in their return to the primary position was evidenced. The patient was not able to voluntarily turn the eyes from the primary position to the left, and following movements were impossible beyond the midline plane in conjugate gaze towards the left (Fig. 3). Medial deviation of

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Fig. 1. Eyes of the patient at rest during the period of forced horizontal conjugate gaze to the right

Fig. 2. Eyes of the patient in upward conjugate gaze during the period of forced horizontal conjugate gaze to the right. He could not deviate the eyes in voluntary or following movements from this plane in conjugate gaze.

Fig. 3. Eyes of the patient in the primary position on the next day. He could not deviate the eyes to the left voluntarily or in following movements beyond the midline plane in conjugate gaze.

Fig. 4. Eyes of the patient in upward conjugate gaze on the same day as in Figure 3

both eyes occurred on voluntary and following movements when convergence was tested. Gross nystagmus was apparent in right lateral gaze, and rotatory nystagmus was apparent in upward and downward conjugate gaze. Voluntary and following movements were preserved in deviation of the eyes toward the right; however, they could not be deviated beyond the midline plane toward the left in upward and downward conjugate gaze (Fig. 4). On attempted closure of the eyelids, the eyes deviated upward in the midline plane. The seventh nerve paralysis was recognized with difficulty.

Forty-eight hours after the onset of these visual symptoms, he had complete return of extraocular eye movements and was free of vertigo. Coarse nystagmus was present when the eyes moved from the primary position.

DISCUSSION

Crosby and associates[1] have revealed relationships that permit clinical localization of the findings of peripheral facial paralysis and a paralytic type of conjugate gaze to a lesion in the pons. This is considered to be located just ventrolateral to the sixth cranial nerve nucleus on the side of the peripheral facial paralysis where the rootlets of the seventh cranial nerve, corticobulbar fibers (abducens division), and corticotegmental fibers are in close proximity to each other.

The transient nature of the seventh nerve paralysis, forced horizontal conjugate gaze, and defect in horizontal conjugate gaze in our patient suggested that localized edema in the area described above had resulted from x-ray therapy. The clinical course of this patient is contrary to Nielsen's rule[2] that a pontine lesion causes permanent conjugate deviation in the paralytic type of lesion.

The neurologic manifestations in this patient are of interest since they suggested certain possible relationships with regard to conjugate gaze in various planes. Anatomical, experimental, and clinical studies by Crosby,[3] Lemmen and associates,[4] and others have revealed supranuclear pathways concerned with voluntary

(corticobulbar fiber pathways and abducens division) and automatic (corticotegmental fiber pathways) eye movements in the horizontal plane. These pathways project onto the contralateral parabducens and abducens nuclei. The abducens nucleus supplies the lateral rectus. The parabducens nucleus discharges through the medial longitudinal fasciculus to the portion of the oculomotor complex supplying the medial rectus on the side opposite the contracting lateral rectus. The observed periods of forced horizontal conjugate gaze and defect in conjugate gaze noted in this case are consistent with involvement of these discharge pathways terminating at the parabducens nucleus. Studies by Crosby and Henderson[5] and others have revealed supranuclear pathways (corticotectal fiber system and corticobulbar system) concerned with conjugate upward and downward eye movements which project onto the superior colliculi. Anatomic and clinical study by Crosby,[3] Rand and Lemmen,[6] and others indicated that the rostral and medial tectal areas are concerned with upward conjugate gaze and the caudal and lateral portions with downward conjugate gaze. The initial period of forced horizontal conjugate gaze reported here suggested the dominance of horizontal conjugate gaze in eye movements, since the supranuclear and midbrain structures concerned with eye movements in the upward and downward conjugate gaze appeared intact. This patient had upward and downward conjugate gaze which was limited to the planes imposed by the forced horizontal conjugate gaze and defect in horizontal conjugate gaze. This demonstrated relationship suggested that while upward and downward conjugate gaze was mediated by the intact midbrain, the range of this type of movement was dependent upon and related to the discharge pathways through pontine structures concerned with horizontal conjugate eye movements.

SUMMARY

Transient periods of forced horizontal conjugate gaze and horizontal conjugate gaze defect with a transient facial paralysis were observed during the course of x-ray therapy of a patient with medulloblastoma of the posterior fossa. The neurologic manifestations suggested relationships with regard to conjugate gaze in various planes.

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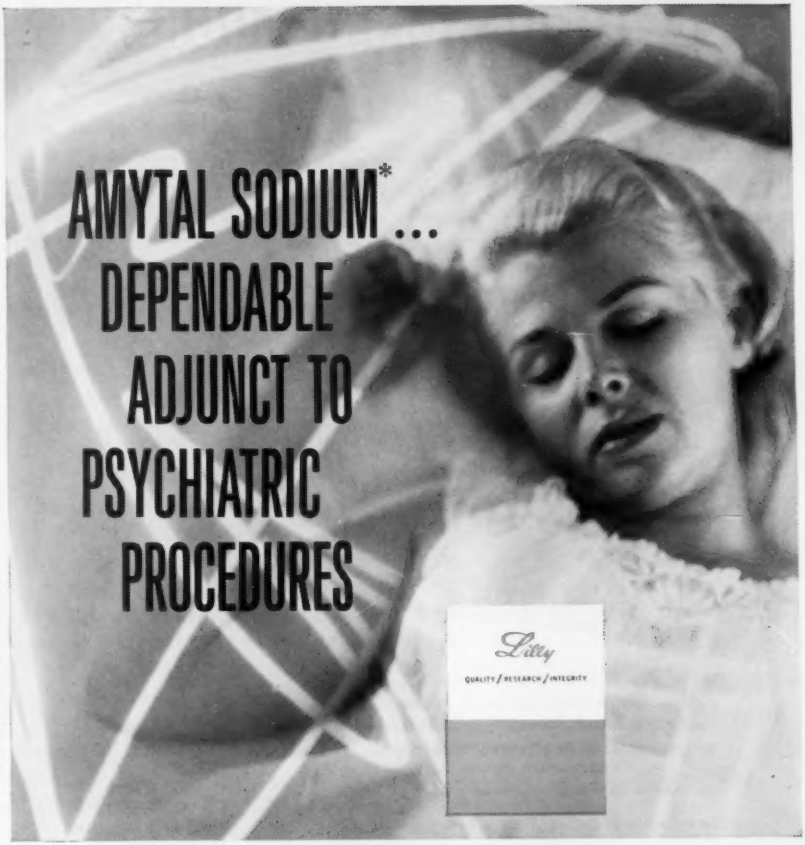

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DECEMBER 1958

York To Be Center Neurologic Meetings

In traditional style, New York City provides the focus for a group of important annual neurologic meetings. On Wednesday, mber 10, the Eastern Association of Electroencephalographers s in the Einhorn Auditorium, Lenox Hill Hospital, 111 East 76th et. Highlight of the program is a 2 p.m. presentation by AAN er, Francis O. Schmitt of the Massachusetts Institute of nology, who will speak on "The Molecular Organization of the e Fiber".... On Thursday, December 11, the sessions of the ican Epilepsy Society begin at the Hotel Roosevelt. Its pro- features a symposium on posttraumatic epilepsy under the rmanship of Wilder Penfield.... On Friday and Saturday, mber 12 and 13, the annual meeting of the Association for earch in Nervous and Mental Diseases is to be held also at the l Roosevelt. The topic under consideration is "Neuromuscular rders".... On Monday and Tuesday, December 15 and 16, the ination of the American Board of Psychiatry and Neurology takes e at the Neurological and Psychiatric Institutes of the mbia University Medical Center. Interspersed between these essional society sessions are the meetings of the Medical ds of several voluntary agencies, the Myasthenia Gravis Foun- on (December 12), Parkinson's Disease Foundation (December and the National Multiple Sclerosis Society (December 14).... annual meeting of the National Committee for Research in ological Disorders (A. B. Baker, Chairman) is scheduled for mber 18 at New York's Hotel Biltmore.

national Symposium in Moscow

An International Symposium, dealing with brain waves and behavior, was held in Moscow, October 6 through 11, 1958. tations were extended by the Soviet Academy of Sciences to ophysiologists from at least 16 countries, including repre- atives from the United States.* The participants reported on r EEG researches, each paper being followed by a formal discus- . The entire proceedings will be published early in 1959.... des attending the Symposium, the participants visited labora- es and clinics in Moscow, Leningrad, Kiev, and Tifflis, where saw at first hand the best in Soviet neurophysiology. During e visits many lively exchanges of views and opinions took place.

tzler, R. Galambos, H. Jasper, H. W. Magoun, F. Morrell and Mrs. Morrell, J. Stevens.

According to participant Robert Galambos, "perhaps such exchanges will become more common under what appears to be a new Soviet policy, namely, to foster and encourage the exchange of scientific personnel between laboratories inside and outside the Soviet Union."

Neurochemical Meetings Held in Europe

Two important meetings of neurochemists were held in Europe in late August and early September. More than 150 scientists from twenty-one countries convened for the Third International Symposium of Neurochemistry in Strasbourg, France, August 25 through 29, 1958. The principal theme of this Symposium, under the general chairmanship of Jordi Folch-Pi, with local arrangements headed by Prof. P. Mandel, was "The Chemical Pathology of the Nervous System," which was divided into the chemistry of metabolic disorders and the biochemistry of mental diseases. According to participant, Donald B. Tower, "the meeting was highly successful and stimulating from the scientific standpoint and was enhanced by the delightful receptions and entertainments provided by the local committee in Strasbourg."..... Another Symposium on the "Biochemistry of the Central Nervous System" was held in Vienna during the Fourth International Congress of Biochemistry (September 1 through 6, 1958). This Symposium, chaired by Prof. F. Brucker (Pharmacological Institute of the University of Vienna), consisted of 14 papers covering various major aspects of current neurochemical problems.... The proceedings of the Strasbourg and Vienna Congresses will be published by the Pergamon Press. Among the Academy members participating in these symposia were: Donald B. Tower, David Nachmanshon, J. Folch-Pi, Jerzy Rose, George Jervis, Harold Himwich, and Alfred Pope.

New Neurological Journal To Be Published

The Academic Press of New York announces the publication early in 1959 of a new journal entitled EXPERIMENTAL NEUROLOGY. The purpose of the journal is to publish scientific papers dealing with reports of experimental investigations in all neurologic disciplines. Case reports, purely descriptive articles, and reviews will not be considered. EXPERIMENTAL NEUROLOGY will be edited by William F. Windle, Chief of the Laboratory of Neuroanatomical Sciences, National Institute of Neurological Diseases and Blindness, who will have as Associate Editors, Sam L. Clark, Edward W. Dempsey, Lewis B. Flexner, Seymour Kety, H. W. Magoun, and Roger Rossiter*.... EXPERIMENTAL NEUROLOGY will be an independent journal of international scope published in the English language bimonthly. It is not affiliated with any individual society or institution. Manuscripts may be submitted to Dr.

*Other members of the Editorial Board are: Raymond D. Adams, A. Bairati, Philip Bard, W. Bargmann, David Brodian, A. Brodal, Edmund V. Cowdry, Elizabeth Crosby, Sir John C. Eccles, John F. Fulton, W. R. Hess, Joseph Hinsey, Bernardo A. Houssay, Holger Hydén, Heinrich Kluver, Sanford L. Palay, Ludo van Bogaert, J. Z. Young.

Windle, Building 10, Room 3D-14, National Institutes of Health, Bethesda 14, Md.

NINDB Mission to Moscow On November 18, 1958, a mission of neurologists and scientists, under the sponsorship of the National Institute of Neurological Diseases and Blindness, left by air for Moscow, via Paris. The purpose of the mission is a thirty-day tour of activities in neurophysiology and neuropharmacology now going on in research institutes in several parts of the U.S.S.R. The members of the team are: Francis M. Forster, Chairman, Louis S. Goodman, Henry W. Woltman, Clinton L. Woolsey, Karl Frank, and Paul I. Yakovlev. The group composes a scientific exchange mission which allows for a return visit of an equal number of Russian scientists to institutions in the United States.... Travel plans and itinerary of the NINDB mission were arranged by the Division of International Health of the Public Health Service, Washington, D.C.

Hill Wins Neurosurgical Award Norman Hill of the Mayo Clinic received the Fourth Annual Award of the American Academy of Neurological Surgery for his paper on cerebrospinal fluid proteins in obstructive lesions of the central nervous system.... The Academy of Neurological Surgery now announces its Fifth Annual Award for the best paper reporting original clinical or laboratory investigations of the nervous system. Eligibility is confined to physicians currently in training in neurologic surgery, or to those who have completed training since June 30, 1957. The recipient will be invited to present his paper at the Twenty-first Annual Meeting of the Academy at Pebble Beach, California (October 18 through 21, 1959). Travel costs, within the North American Continent, expenses while attending the meeting, and an honorarium of $100 will be paid.... Manuscripts with a resume of the candidate's postdoctoral training should be submitted before July 15, 1959, to Dr. Robert McLaurin, Secretary of the Academy, Cincinnati General Hospital, Cincinnati 29.

Rembolt Becomes President-Elect of Cerebral Palsy Group At the Twelfth Annual Session of the American Academy for Cerebral Palsy at the Sheraton-Biltmore Hotel in Providence, Rhode Island, Raymond R. Rembolt was elected President-Elect of the Academy. Other officers elected were: Temple Fay, Vice-President, Glidden L. Brooks, Secretary, and Samuel B. Thompson, Treasurer. The Academy's incoming President is Alvin J. Ingram who succeeded William T. Green.... The 1959 meeting of the AACP will be held at the Hotel Statler in Los Angeles, November 30 to December 2, 1959. As of January 1, 1958, the membership of the AACP totaled 231. At the Providence meeting, 31 additional Fellows and Associate members were added to the membership roster and one Foreign Corresponding member, Bjarne Andersen of Oslo.

Briefs E. R. Squibb & Sons celebrated their centenary in October 1958 by sending Macdonald Chitchley on a lecture tour through the medical colleges of Richmond, North Carolina, Tulane, Tennessee, and Baylor. The topic of Critchley's "Squibb lecture" was "The Study of Language Disorders: Past, Present, and Future" .... An extended talking tour has been arranged for Sir Francis Walshe of London this spring. His itinerary includes stops in Cincinnati, St. Louis, San Francisco, Baltimore, and Bethesda.... Beginning December 27, 1958, A. B. Baker will embark on a Fulbright teaching fellowship (6 months) in order to lecture at the University of Oslo and to neurologic societies in the Scandinavian countries.... Charles M. Pomerat, Professor of Cytology at the University of Texas, will give the annual Israel S. Wechsler lecture in the Bloomenthal Auditorium of the Mount Sinai Hospital, New York City, on December 12, 1958. The subject of his presentation is "Recent Advances in the Study of Living Nerve Tissue".... Rhett Talbert, Assistant Professor of Neurology at the Medical College of South Carolina has returned from his tour in Halifax, Nova Scotia, where he was engaged in evaluating patients in that area in connection with a study of the geomedical aspects of multiple sclerosis.... Erna Gibbs was the recipient of the Eminent Achievement Award of the American Woman's Association, presented at a special luncheon on November 22, 1958, in the Waldorf-Astoria Hotel in New York.

Percy Bailey

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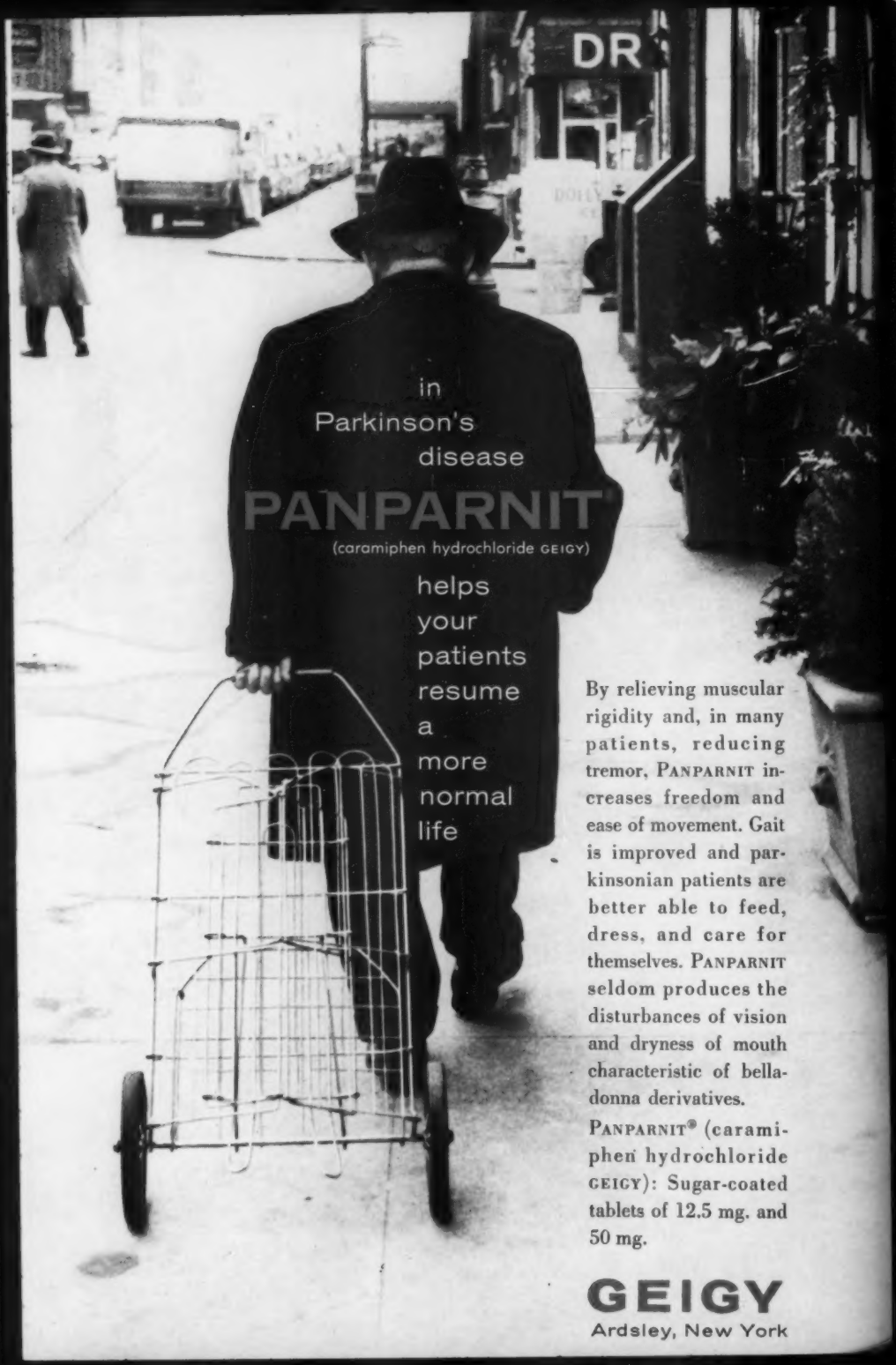

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